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MASKED AND PSEUDO-ASTHMA

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IN the routine practice of allergy the establishment of a diagnosis of bronchial asthma is rarely difficult. Usually the patient offers this diagnosis as his presenting symptom. We must therefore be alerted to avoid the resulting pitfalls this engenders and to escape the trap set by these patient-labelled symptoms which tend to dull our diagnostic acumen.

The following case reports are offered because of their interest from the diagnostic viewpoint and their relative infrequency in the practice of clinical allergy. This latter fact is attested to by the little reference material on these subjects in the literature on allergy.

MASKED ASTHMA

Trowbridge[8] in 1944 reported that Maccone in a review of world literature to 1940 collected only twenty-seven cases of spontaneous pneumothorax complicating bronchial asthma. He made the following pertinent observation: "The large number of interesting medical and surgical methods of treating bronchial asthma tend to direct one's attention toward therapy rather than toward a consideration of a possible concomitant pathologic process."

Van Ordstrand,[9] in considering the subject of idiopathic spontaneous pneumothorax, cited Kirshner's triad of etiologic agents, as infectious, congenital, and pleural emphysematous blebs, the latter being most practicable and widely accepted.

In a review entitled "The Common Pulmonary Diseases" appearing in the *Lederle Bulletin*,[2] the pathogenesis of spontaneous pneumothorax was considered. In 105 consecutive cases observed at Columbia-Presbyterian Medical Center, in eight only was disease of the lungs or pleura present (six with pulmonary tuberculosis, one with pleural carcinomatosis, one with suppurative pleurisy). Pleural effusion was present in 47 per cent of the cases, but tuberculosis developed in no patient who was not tuberculous at the time of the attack. McKay suggested that in many cases spontaneous pneumothorax developed as a result of mediastinal emphysema.

Spontaneous Pneumothorax Masking Bronchial Asthma

Case 1.—E. E. M., forty-one, a white male coal miner, was presented for treatment in March, 1951.

Fig. 1. Case 1. *(a)* Anterior view. Note tendency to pigeon-breasted deformity. *(b)* Lateral view. Note increased anteroposterior diameter and barrel-chested deformity.

The essential features of the history were as follows. This patient had been suffering from bronchial asthma for approximately the past twenty-five years. The asthma was perennial in character but was always worse during the late summer and fall months. The symptoms of respiratory embarrassment became progressively worse and were especially severe while working in the mines. There was a progressive loss in weight amounting to fifty pounds during the past year. In December, 1950, he developed a pain in the left chest which followed an upper respiratory infection for which penicillin had been administered. He was hospitalized at the Grafton City Hospital, Grafton, West Virginia.

On February 15, 1951, he was transferred to the Montefiore Hospital, Pittsburgh, Pennsylvania.

On examination this patient appeared to be emaciated. The nose showed evidence of a marked deviation to the right with almost complete obstruction from the septal deviation and edema of the turbinates. The chest showed evidence of a marked barrel-shaped deformity (Fig. 1*a* and *b*). The breath sounds were almost absent over the entire left chest. Marked emphysema and hyperresonance were present. The heart tones were barely audible. The remainder of the examination was essentially negative.

The clinical impressions were as follows: (1) chronic bronchial asthma with emphysema, and (2) left pneumothorax, possibly from a ruptured emphysematous bleb. It was necessary to consider the following possibilities: tuberculosis, bronchogenic tumor, and bronchiectasis.

The laboratory findings were as follows:

C. B. C. (Feb. 16, 1951).—Hgb: 14.5 gm or 96%; WBC: 9,300; RBC: 4,900,000; Polys: 67%; Lymph: 33%.

Urinalysis (Feb. 16, 1951).—Albumin—negative; Sugar—negative; Reaction—pH 5.5; Specific gravity: 1.009; Microscopic: Occ. WBC.
Sedimentation rate—30′—4 mm 60′—8 mm MSR—½ mm
Wasserman and VDRL—negative
Tuberculin test (intradermal and patch)—negative

Sugar—85 mg per cent N.P.N. 33 mg per cent
Daily sputum cultures (Feb. 17-23, 1951) were negative for acid-fast organisms and fungi.

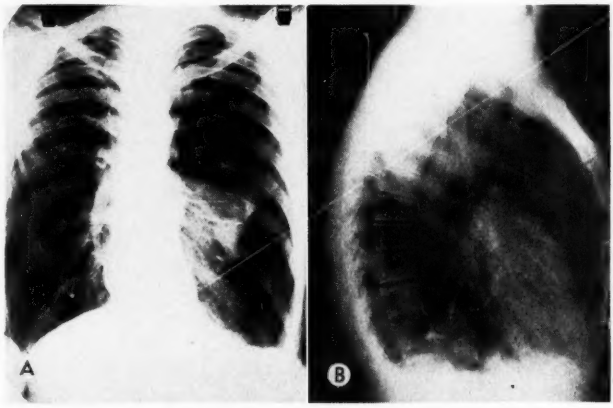

Fig. 2. Case 1. February 16, 1951. *(a)* Posteroanterior view. Note extensive left pneumothorax and pleural effusion; also tension diaphragm. *(b)* Lateral view. Note pneumothorax, barrel-chested deformity, and increased radiolucency of anterior mediastinum.

Nasal smear (Feb. 22, 1951)—no eosinophils seen. Sputum—no acid-fast organisms seen in direct smears; predominating organisms Gram-positive diplococci, cocci, and rods.
Direct smear during bronchoscopy (Feb. 24, 1951)—no tumor cells seen. No acid-fast organisms. Predominating organisms Gram-positive cocci.

Electrocardiogram.—Abnormal electrocardiogram—low voltage in precordial leads. Electrical position—vertical with clockwise rotation.

Bronchoscopy (Dr. S. E. Penn).—Under local anesthesia of 10 per cent cocaine and 1 per cent pontocaine, a 7 x 40 bronchoscope was passed. The larynx and carina were normal.
Right main bronchus.—The lower middle and upper lobes were well visualized and showed no evidence of any growth or infection.
Left main bronchus.—Examination of the left bronchus revealed collapse of the left upper lobe. Large amounts of mucoid secretion came from the left upper lobe, which was aspirated. The left lower lobe revealed no evidence of any obstruction or infection.
Bronchial secretions were sent to the laboratory for study.

Roentgenographic Findings—Feb. 16, 1951—(Fig. 2*a* and *b*).—The radiographs showed spontaneous pneumothorax on the left side of the chest with collapse of the lung against the left border of the heart and with some rotation of the heart. The chest was markedly emphysematous in character, and at the right apex there was some haziness and, in addition, two small rounded shadows of lessened density, which suggested a cavity at that point. Some slight lipping on the dorsal vertebrae was noted, suggesting a hypertrophic osteoarthritis.
Fluoroscopic and stereoscopic examination of the chest, (Feb. 20) as well as lateral projections, revealed very little change since the previous examination. There was a slight increase in the amount of fluid at the left base. The collapse of the lung remained essentially unchanged. Stereoscopy of the findings in the right apex again revealed the increased density at that point and the very small area of lessened density, which suggested a small cavity rather than an emphysematous bulla.
Sinuses (Feb. 23).—The sinuses were essentially negative. There was a slight increase in density in the left antrum suggesting a thickening of the membrane at that point but subclinical in character.

Chest (Feb. 24).—The appearance of the chest remained essentially the same as was noted at the original study on February 16, 1951. There was apparently no

decrease in the amount of air in the pleural cavity nor in the expansion of the lungs. There was a slight increase in the amount of fluid in the left pleural cavity at the base.

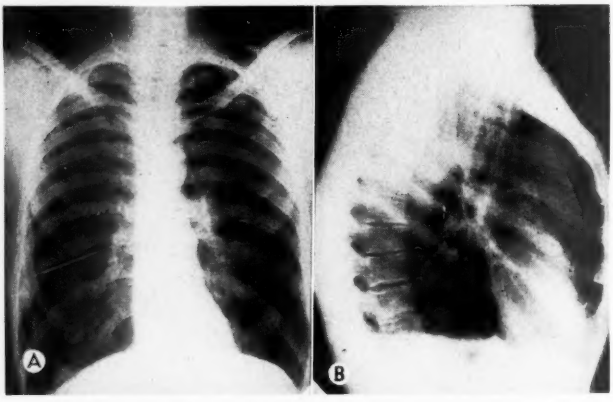

Fig. 3. Case 1. April 16, 1951. *(a)* Posteroanterior view. Note almost complete re-expansion of lung and resorption of fluid. *(b)* Lateral view. Note fluid level posteriorly not seen in posteroanterior view.

Allergen tests were performed to the inhalants, including dust, pollen, molds, foods, and bacterials. The following reactions were obtained:

Marked positive reactions were obtained to house dust, dog dander, spinach, apricot, and vanilla.

Positive reactions were obtained to feathers, horse serum, tobacco, white potato, radish, egg white, oats, rice, chocolate, string bean, tomato, blackberry, walnut, canteloupe, cherry, grapefruit, scallop, whitefish, peanut, honeydew, lemon, prune, strawberry, and molds (Alternaria, Aspergillus, and Penicillium).

Doubtful positive reactions were obtained to English plantain, wool, glue, rabbit dander, rye, liver, pork, lima bean, mushroom, onion, corn, cucumber, garlic, green pea, asparagus, beet, cabbage, carrot, clam, banana, cocoanut, herring, pear, and plum.

Immediate marked positive reactions were obtained to Friedlander bacillus, diphtheroid bacillus, pneumococcus, *Micrococcus catarrahalis*, Staphylococcus, pertussis bacillus, and influenza bacillus.

Delayed positive reactions were obtained to pneumococcus and pertussis bacillus.

The patient was discharged from the Montefiore Hospital on February 25, 1951.

He was observed for follow-up studies at the office during March. The involved lung appeared to be slowly re-expanding. The fluid level in the left base remained essentially as noted previously. He began to show symptomatic improvement, dyspnea being almost entirely absent. The vital capacity was 3.6 liters, or 73 per cent.

During his office visits, penicillin aerosol inhalations with oxygen were administered. Desensitization with house dust and molds and respiratory vaccine was instituted. He was also placed on symptomatic medication including iodides.

X-Ray Report April 16, 1951 (Fig. 3, *a* and *b*).— Fluoroscopic, P.A., and lateral films of the chest revealed a hydropneumothorax on the left. The left lung was about 80 per cent expanded. In comparison with the previous study it revealed the left costophrenic sulcus to be clear, indicating that most of the fluid had been absorbed. The fluid was now confined to the posterior gutter. There was questionable evidence of a lesion in the superior portion of the left lung, but I did not think that a lesion could be definitely diagnosed until the lung was fully expanded. There was a pleural thickening in the right apex with a small focus of increased density

which had not changed since the previous examination. Marked generalized emphysema was present.

X-Ray Report Sept. 10, 1951 (Fig. 4).—Fluoroscopic and radiographic oblique and posteroanterior views of the chest in comparison with previous studies revealed the left lung to be completely re-expanded. There remained no evidence of fluid.

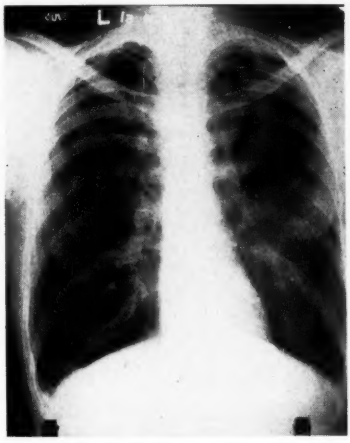

Fig. 4. Case 1. September 10, 1951. Posteroanterior view. Note complete re-expansion of the lung.

Thickening of the apical pleural caps was present bilaterally. There was no evidence of a parenchymal lesion. The marked generalized emphysema was again noted.

On December 3, 1951, the chest was entirely clear and the vital capacity was 4.6 liters, or 99 per cent.

This patient was last seen in March, 1952. He has maintained complete expansion of the lungs and has been entirely free of asthmatic respirations. He has shown a steady weight gain. The vital capacity was 4.8 liters. Plans are being made to perform the required corrective nasal surgery.

Summary.—Surprisingly, the occurrence of massive spontaneous pneumothorax complicating bronchial asthma is not frequently encountered.[5,7] This case is therefore reviewed indicating the steps in differential diagnosis, technique of management, and follow-up examination.

PSEUDO-ASTHMA

It may sound trite to repeat the well-known dictum that "all is not asthma that wheezes." However, the clinical importance of the oft and glibly repeated aphorism cannot be overemphasized. Many of these patients unfortunately will masquerade as cases of bronchial asthma for several years until the underlying pathologic process has reached an irreversible and helpless progression. A keen ear, training, and clinical experience are necessary to assist in recognizing the slight alteration in the wheezing respiration that distinguishes it from the allergic wheeze. The changing character of the wheeze may suggest the need for endoscopic investigation.

It is not within the scope of this paper to review all the causes of asthma-

toid respirations. Our colleagues in the field of otolaryngology deserve great credit for their contributions in this field.[1,3,4,6]

The following report is an example of a case of pseudo-asthma.

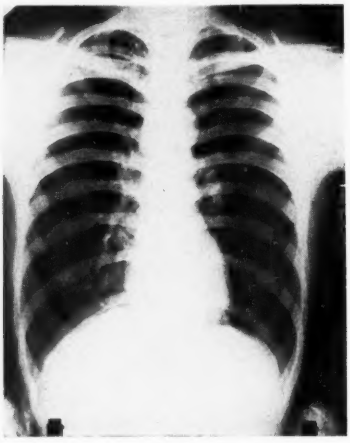

Fig. 5. Case 2. Negative findings except for healed foci. Note paratracheal nodes.

Endotracheal Papillomata Causing Pseudo-asthma

Case 2.—W. P., a twenty-one-year-old male coal miner, complained of "bronchial asthma" for the preceding five years. The "asthma" developed several months following the removal of a tracheal polyp. His asthmatic symptoms were perennial and were always worse during damp weather and temperature changes. He became progressively worse throughout the years and suffered from fairly constant dyspnea, wheezing, and cough. These symptoms had prevented him from working regularly for some time. In addition he suffered from occasional nasal blockage and postnasal secretion. He also had impairment of the appetite and self-imposed restriction of food intake, resulting from dysphagia as revealed by the history. The remainder of the history was essentially negative except for an episode of multiple joint pains one year previously, for which he was confined to bed for several days.

A striking feature of the physical examination was the presence of a marked inspiratory stridor with associated depression of the supraclavicular fossae. A postoperative scar from a previous tracheotomy was apparent. Blood pressure was 120/90. Height: 67¾ inches. Weight: 129½ pounds.

Examination of the nose and accessory sinuses revealed the presence of a deviated nasal septum, edematous nasal turbinates, and cloudiness of both antral sinuses on transillumination.

Physical and fluoroscopic examination of the chest revealed the heart to be within normal limits. The respirations were shallow, and expiratory wheezes were audible throughout the lung fields. Increased peribronchial fibrosis was noted. The diaphragm was depressed. The vital capacity was 3.6 liters, or 83 per cent. The remainder of the examination was essentially negative.

The patient was referred to another physician for laryngoscopic and bronchoscopic examination. He reported the presence of a large subglottal tumor for which he recommended immediate surgical removal and biopsy studies.

Roentgenologic Findings—June 7, 1951—Montefiore Hospital, Pittsburgh, Pa. (Fig. 5).—The chest was essentially negative, there being no evidence of active pathology therein. There was a small rounded shadow of increased density in the region of the larynx, which rather strongly suggested the possibility of a neoplasm at that

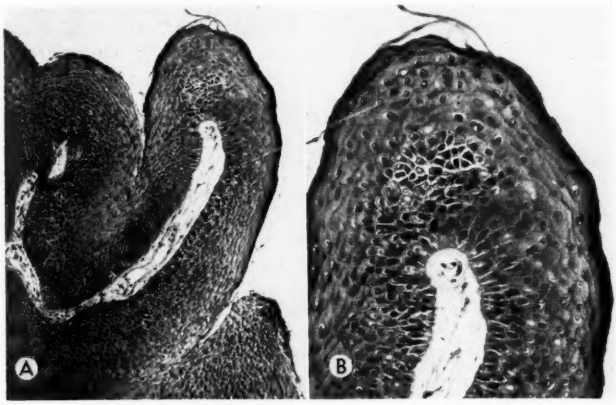

Fig. 6. Case 2. *(a* and *b)* Endotracheal papilloma showing papillary projections lined by several layers of epithelium, mostly spindle type, and with occasional mitoses.

point. Following the administration of barium by mouth, the barium passed down the esophagus without meeting any delay or obstruction, and no additional information of value was derived concerning the larynx or trachea.

The patient was admitted to the Montefiore Hospital, Pittsburgh, on June 6, 1951. A tracheotomy was performed and biopsy specimens were obtained from the endotracheal tumor. These were reported as being papillary projections lined by several layers of epithelium, mostly spindle type, with occasional mitoses (Fig. 6*a* and *b*). The bronchoscopist observed these tumorlike masses to be present downward along the trachea below the tracheotomy level. The tumor was of such character and extent that surgical removal was not considered to be desirable.

He was placed on antibiotic therapy with penicillin and aureomycin. During his period of hospitalization all clinical evidence of bronchial asthma disappeared, and the patient stated that symptomatically he was considerably improved—more so than at any time in the previous several years. The possibility of x-ray therapy to the lesion was considered but had not yet been undertaken. The patient was discharged from the hospital on June 20, 1951, with a tracheotomy tube in position.

Later he was referred to the Memorial Hospital, New York City, where a laryngotracheo fissure was performed on October 15, 1951. The report was as follows: "The papilloma was found to be extensive and bled easily on manipulation. The lesion seemed to be growing from the superficial layers of the mucosa, and was removed with biopsy forceps. Electrocautery of low current was used to destroy the base of each area of the papilloma. It was estimated that about 30 per cent of the trachea, mostly the anterior and lateral surfaces, was removed. It was not necessary to open the chest, as the lower portion of the growth could be reached from above. The lowermost portion of the growth was about four to five centimeters from the carina. The outlook for this patient was uncertain. Most likely he will have recurrences from the papillary growth, and they could be removed as they arise, through the bronchoscope. However, the possibility of carcinoma arising from these papillomata must always be kept in mind."

This may be considered as a case masquerading as bronchial asthma to which the term pseudo-asthma is applied. The patient felt he was suffering from chronic bronchial asthma. When first seen by me, he appeared to be in imminent danger of asphyxia from a large subglottal tumor. An emergency tracheotomy was performed, followed by subsequent surgical removal of endotracheal papillomata.

When last seen several weeks ago, he appeared in excellent health, having made a remarkable weight gain and having no evidence of impaired or altered respiration.

CONCLUSION

Two coal miners with long-standing histories of bronchial asthma were referred for allergic investigation and management. Each offered major presenting symptoms which led to the establishment of the ultimate diagnosis: in one instance spontaneous pneumothorax, in the other endotracheal papillomata. It is interesting to note how relatively infrequently these latter clinical entities are encountered in the routine practice of allergy.

The paper concerns itself with review of the case reports and emphasis on the features of differential diagnosis and management.

Case 1.—Spontaneous pneumothorax developed in a forty-one-year-old coal miner with a twenty-five-year history of bronchial asthma. Following an upper respiratory infection he developed a persistent pain in the left chest. After complete studies, diagnosis was made of spontaneous pneumothorax possibly following the rupture of emphysematous blebs. The studies included bronchoscopic aspiration and examination, serial x-rays, repeated sputa examinations, and guinea pig inoculations to rule out tuberculosis. Follow-up studies were carried out until there was complete re-expansion of the infected lung. Because the occurrence of spontaneous pneumothorax with bronchial asthma is not common, it is felt that the presentation of such a case would be of interest.

Case 2.—This is a twenty-year-old coal miner who presented a history of bronchial asthma for five years which first developed several months following removal of an endotracheal polyp. When he was first seen, he appeared to be in imminent danger of asphyxia from a large obstructive subglottal tumor. An emergency tracheotomy was performed. Later studies revealed the tumor to be endotracheal papillomata. Surgical removal of the main portion of this mass was undertaken. This represents a case that might be considered under the class of pseudo-asthma, and the diagnosis again emphasizes the old well-known dictum of Osler that "all is not asthma that wheezes."

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CONSTANT PERCENTAGE INCREMENT OF ANTIGEN DOSAGE FOR DESENSITIZATION IN ALLERGIC DISEASES

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THE increments of antigen dosage in a series of injections for desensitization in allergic diseases frequently show wide percentage variations in relation to the antecedent doses. The larger percentage increments most often appear early in the course of treatment—e.g., doses of 0.1 cc, 0.2 cc, 0.3 cc, and 0.4 cc, having increments of 100 per cent, 50 per cent, and 33 per cent respectively. This would appear to be a reversal of the expected tolerance of the patient if desensitization is being accomplished. A constant percentage increment of antigen from dose to dose throughout a series of injections appears to be more desirable. This may be provided by an adaptation of the Fibonacci series of numbers. Pierce[1] has presented an interesting account of this unusual series and its wide implications in nature, in science, and in art.

This series, which is of the form

$$u_n = u_{n-1} + u_{n-2}$$

may be developed from the less cumbersome equation

$$x = y + y'$$

by letting x, y and y′ equal respectively u_n, u_{n-1}, and u_{n-2}. In it y and y′ are the last two numbers developed in the series and x the new number to be added. To begin the series, the value 2 may be assigned to y, and 1 to y′. By substitution the equation becomes

$$x = 2 + 1, \text{ or } 3$$

This provides the first three numbers of the series 1, 2, 3. The value of y now becomes 3, and that of y′ 2, so that

$$x = 3 + 2, \text{ or } 5$$

which becomes the fourth number of the series, 1, 2, 3, 5. If these numbers are set in a vertical column, each new number (x) is easily determined by adding the last two numbers showing in the series, as follows:

y′— 1
y — 2 — y′
x — 3 — y
5 — x
8
13
21
34
55
89
144
233
377
610, et cetera

Returning to the equation,

$$x = y + y'$$

it is apparent that y′ is the increment which when added to y produces x. From the above series, y′ may be calculated as a fractional part of y. If y and y′ are chosen at different stations in the series as it develops, y′ varies widely at first but consistently approaches a fixed value in terms of y, which can be shown to be .618034 y. This appears to be a most remarkable feature of any series of numbers developed from this equation, e.g.:

(1) $\frac{y'}{y} = \frac{2}{3}$, or $y' = .666667\ y$ (2) $\frac{y'}{y} = \frac{3}{5}$, or $y' = .600000\ y$

(3) $\frac{y'}{y} = \frac{5}{8}$, or $y' = .625000\ y$ (4) $\frac{y'}{y} = \frac{8}{13}$, or $y' = .615385\ y$

(5) $\frac{y'}{y} = \frac{13}{21}$, or $y' = .619048\ y$ (6) $\frac{y'}{y} = \frac{21}{34}$, or $y' = .617684\ y$

(7) $\frac{v'}{y} = \frac{34}{55}$, or $y' = .618182\ y$ (8) $\frac{y'}{y} = \frac{55}{89}$, or $y' = .617978\ y$

(9) $\frac{y'}{y} = \frac{89}{144}$, or $y' = .618056\ y$, et cetera (10) $\frac{y'}{y} = \frac{144}{233}$, or $y' = .618026\ y$, et cetera

y′ decreasing, or alternately increasing, toward .618034 y.

Any value may be assigned to y or y′ at the beginning of such a series. The terms of the series will differ accordingly, but as each series is extended, y′ approaches and eventually becomes .618034 y. It follows that any dosage schedule may gradually be converted into a constant percentage increment series by repeatedly using the sum of the last two doses as the new dose, but in order to have this condition apply from the beginning a value must be assigned to y′, which is .618034 y, or 61.8 per cent of y. These relationships would be established:

y equals 1.000000
y′ equals .618034 y, or .618034
x equals 1.618034 y, or 1.618034

By using these values, a schedule of dosage for any dilution of antigen may be set up. It will have a constant increment from dose to dose of 61.8 per cent. The individual doses may be kept small enough to be administered with a tuberculin syringe by the proper choice of dilutions of the antigen, as follows:

Antigen Dilution 10^{-n}

y'.....06	18034	cc*
y 10	60000	cc
x 16	18034	cc

.26 cc
.42 cc
.68 cc.....Antigen Dilution $10^{-(n-1)}$

.11 cc
.18 cc
.29 cc
.47 cc
.76 cc, et cetera

It is not likely that in any given patient the progression of dosage will follow the tabulation without interruption. The dosage must be adjusted to the patient. In our work with rheumatic diseases, three considerations have been helpful in bringing about these adjustments:

1. Starting the treatment with infinitely small doses.

2. Regulating the intervals so that they are roughly proportional to the size of the doses up to a limit of three or four weeks, according to the effective range of the antigen used.

3. Repeating or reducing a given dose if unfavorable reaction follows its use. This may be accomplished within the scope of the tabulated series without disturbing its interrelations.

GRAPHS OF ANTIGEN DOSAGE

The presentation of data on the dosage of antigen by direct graphs is not practical if the range of dosage is as wide as that usually required in allergic diseases. They may be used for short runs of the tabulated series, or for the longer periods of treatment which require infrequent increases of dosage.

Logarithmic graphs may be used for longer runs of the tabulated doses. Since the logarithm of 1.618 is 0.2089, the plotting factor of the elevation in these graphs from dose to dose would be 0.2. Direct and logarithmic graphs are illustrated in Figures 1 and 2 respectively. Logarithmic plotting of dosage may be carried through twenty-four doses of antigen, involving five dilutions, before the accumulated error caused by dropping .0089 from the logarithm of 1.618 amounts to a .2 plotting unit. This may be adjusted by introducing a "leap" unit of .4 after each twenty-four

*Volume measurements are limited to hundredths of a cubic centimeter in the tuberculin syringe, and consequently the increments will deviate somewhat from this mathematical constant, when third place decimals are interpolated to the nearest hundredth of a cubic centimeter. Table I shows this deviation to be less than ±5 per cent if doses of antigen of, or above, 0.1 cc are used. With doses of antigen of, or below, 0.05 cc, the deviation would be ±10 per cent and upwards. The error varies inversely with the size of the dose of antigen and becomes negligible with the doses in positions D and E in the table.

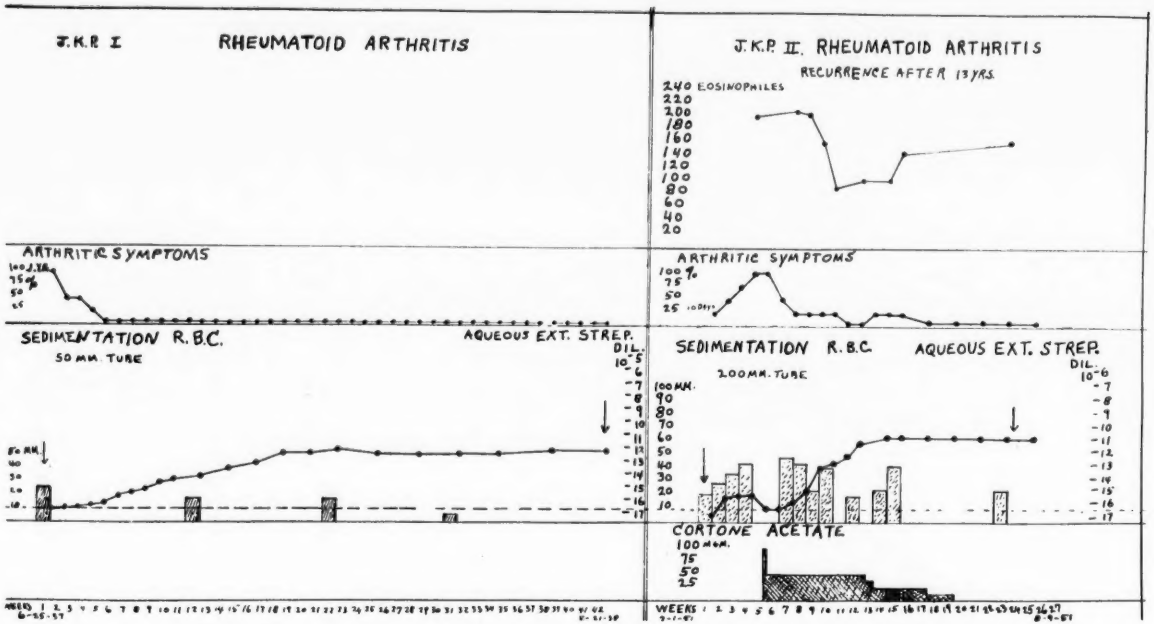

Fig. 2. (I) J. K. P., a thirty-nine-year-old woman with rheumatoid arthritis for one year. A.E.S. treatment started June 25, 1937. Discharged April 21, 1938. Logarithmic graph of A.E.S. dosage.

(II) Recurrence after thirteen years at age of fifty-two years. Minimal amount of Cortone. A.E.S. treatment throughout. Logarithmic graph of A.E.S. dosage.

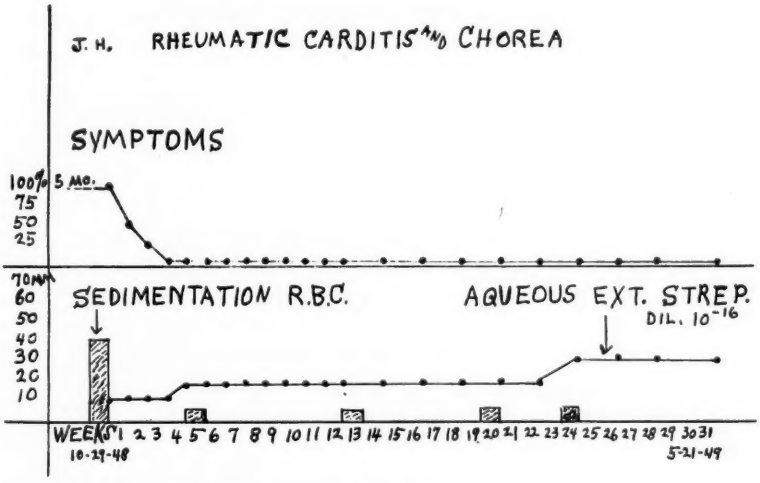

Fig. 1. J. H., a thirteen-year-old schoolboy with rheumatic carditis and chorea. Direct graph of A.E.S. dosage at three levels only and at intervals of seven, fourteen, twenty-one and twenty-eight days over a total treatment period of nineteen months. The first thirty-one weeks are charted.

stations in the plot. A blank space in Table I indicates where this may be done. Using dilutions capable of being designated by the negative exponent, which is the equivalent of a logarithmic designation, simplifies reference to them and facilitates the plotting of logarithmic graphs. In these the first dose under each dilution (Table I) may be set up at an elevation of ten small squares on co-ordinate paper above its contingent lower dilution. The five doses under each dilution then occur at elevations of two small squares each until the twenty-fifth dose, where an elevation of four squares is indicated to overcome the accumulated error mentioned above. By utilizing Table I, therefore, extended logarithmic graphs may be made without the necessity of consulting logarithm tables.

DISCUSSION

This system of dosage is presented because of its simplicity, flexibility, and convenience of recording. In adapting dosage to the patient, it is not to be expected that each may at all times be given doses of 61.8 per cent increments. This increment may easily be divided by advancing from dose to dose of Table I by two or more equal stages: e.g., .26 cc to .42 cc dosage advance may be accomplished in quarter stages—.26, .30, .34, .38, and .42 cc. Likewise, double jumps may be used in advancing dosage more rapidly: e.g., .10, .26, .68 cc, etc. To retain the conveniences of Table I in recording dosage of antigen, it is only necessary to include in the modi-

TABLE I.

SCHEDULE OF DILUTIONS OF ANTIGEN AND VOLUME DOSAGES OF EACH

Dilutions of Antigen*							Position	Maximum Deviation from Standard Increment, 61.8%
10^{-18} 10^{-13} 10^{-8}	10^{-17} 10^{-12} 10^{-7}	10^{-16} 10^{-11} 10^{-6}	10^{-15} 10^{-10} 10^{-5}	10^{-14} 10^{-9} 10^{-4}	10^{-3}	10^{-2}		
cc	cc	cc	cc	cc	cc	cc		
.10	.11	.12	.14	.15	.10	.11	A	E to A +4.9%; −3.9%
.16	.18	.20	.22	.24	.16	.18	B	A to B +4.9%; −4.7%
.26	.29	.32	.36	.39	.26	.29	C	B to C +1.8%; −1.8%
.42	.47	.52	.58	.63	.42	.47	D	C to D +0.8%; −0.7%
.68	.76	.84	.94	—	.68	.76	E	D to E +0.3%; −0.3%

*The exceptionally wide range of dilutions is presented to include the micro-dosage of PPD tuberculin (purified protein derivative) in tuberculosis and the aqueous extract of streptococci (AES)[2] used by the authors in the rheumatic diseases. Beginning doses of AES for rheumatoid arthritis are usually of the 10^{-18} dilution, for chorea and rheumatic carditis of the 10^{-16} dilution, and for hypertrophic arthritis and fibrositis of the 10^{-13} dilution. Volume dosage of the stronger solutions of antigens—1:10,000, 1:1,000, and 1:100—are found in the vertical columns to the right in the tabulation under dilutions 10^{-4}, 10^{-3}, and 10^{-2} respectively.

fied schedules the doses indicated in it, so that they may serve as key points in the plotting of graphs.

The practical application of accurately calculated doses involves a number of considerations which tend to impair accuracy of volume dosage. Even the best syringes calibrated to deliver hundredths of a cubic centimeter are not certified as to accuracy. This may introduce substantial errors in measuring small amounts of antigen. The inaccuracies introduced in a schedule of doses calculated on the basis of four decimals, when reduced to two decimals to accommodate measurements in the syringe, are presented in Table I. These errors may be reduced through the use of the larger volume doses. With the use of doses of less than 0.1 cc, they are so great as to nullify any system of accurately calculated dosage.

Each syringe when a solution is drawn into it has a "dead space" in the tip of the syringe and in the needle attached. This is filled with solution, but the amount contained is not registered on the calibration. As long as this "dead space" remains filled with the solution of antigen no inaccuracy of dosage is introduced, but when a diluent is drawn into a syringe after it already contains a measured dose of antigen, that antigen which was contained in the "dead space" enters the calibrated portion of the syringe and introduces a considerable error especially in the measurement of the smaller doses.

Volume dosage is but one of the two great variables in the desensitization technique. Fortunately it is governed by the exact physical sciences of mathematics and mensuration. A most careful technique is the best assurance of attaining a reasonable degree of accuracy with volume dosage.

The second great variable in desensitization is that of the time interval between the doses employed in a course of treatment. This is governed by biologic laws which cannot be reduced to an exact science. Each dose of antigen introduced parenterally into an allergic individual must be "processed" to bring about desensitization. The time required for this

processing is unknown, but there are indications that it is relatively short as compared with the duration of the benefits arising from such processing. Effective dosage may be raised or lowered by shortening or lengthening respectively the intervals between treatments. Successful desensitization may be accomplished quickly or slowly depending upon the spacing of the doses of antigen. In this phase of the work, experience on the part of the physician is paramount.

There appears to be a top or ceiling dosage of antigen for each individual which may be governed by factors of both volume dosage and the spacing of doses. This is an amount of antigen beyond which a worsening of the patient's condition occurs. When this is reached in volume dosage, the attempt should be made to determine an optimal dosage at a lower level of volume. The identification of ceiling dosage should facilitate the determining optimal dosage, which latter, we believe, is the signal for spacing the doses at longer intervals. Just as there is a ceiling dose for the patient, there is also a time limit through which the optimal dose of each type of antigen is operative. This has been referred to above as the effective range of the antigen. In our work with the rheumatic diseases, intervals up to four or five weeks are frequently practiced year in and year out without significant further change in volume dosage.

Ceiling dosage is illustrated in the plotted dosage in Part II, Figure 2, and was met by lowering the volume dosage of antigen and by the supplementary use of cortisone. Optimal dosage with lengthened intervals between treatments is shown in both Figures 1 and 2 as the dosage curves level off. In rheumatic carditis the optimal dosage of antigen is usually readily identified, and thereafter only the spacing of the treatments requires adjustment over prolonged periods.

SUMMARY

It is believed that the system of antigen dosage presented will facilitate both the treatment of allergic diseases and the recording of the patient's progress.

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DRUG ALLERGY—SOME CLINICAL AND IMMUNOLOGICAL ASPECTS

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SEVERAL million people in this country suffer, have suffered, or will suffer from allergic reactions to drugs. The symptoms vary from the temporary annoyance of simple rashes to more prolonged and disabling "serum sickness" type of reactions, serious involvements of blood-forming organs, and even fatal diseases such as polyarteritis and other visceral changes. The incidence and seriousness of allergy to drugs of known identity are sufficiently important to deserve attention in their own right. But to this must be added the possibility that in addition to this allergy to labelled drugs and chemicals many persons may experience acute or chronic allergy from other just as simple chemicals present in food, in the air, and perhaps intrinsically; these cannot be labelled at the present time. This paper is not intended to be an exhaustive and detailed review, such as has been done so splendidly by Brown,[4] Carr,[5] Sherman[37] and others. Its purpose rather is to attempt to co-ordinate the salient highlights observed clinically and experimentally and to stimulate interest in investigation in this important field.

Pharmacologic or toxic effects must not be confused with true allergy. An allergic reaction to a drug does not occur on first exposure to it. It is possible for the "second" exposure to be that portion of the drug which has not been eliminated several days following its administration (penicillin, serum). It is also possible that the first exposure may have taken place *in utero* or by the ingestion of breast milk. The manifestations are not peculiar to the drug but consist of such symptoms as are commonly recognized as allergic and also produced by other drugs and other antigens. Thus, a heightened sensitivity to quinine resulting in tinnitus from small doses is an increased pharmacologic sensitivity and not an allergy. It is true that some drugs have a greater propensity for producing certain types of allergic reactions, such as aminopyrine producing granulocytopenia. The amounts required to provoke an allergic reaction are usually much smaller than those necessary for the pharmacologic effect. With most drugs only a fraction of the population react with allergic symptoms, although certain chemicals (1-2-4 dinitrochlor-benzene) are such potent sensitizers that they can induce an allergy in all experimental subjects.[44] Specificity is marked, is often of group variety, but is dependent on the chemical structure rather than on the pharmacologic action of the drug.

For the purpose of the present discussion those therapeutic products

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which are proteins or other complex substances, such as serum, insulin, and liver, will be omitted from consideration. The problem of allergic dermatitis resulting from contact with chemical substances will be only briefly mentioned, since the subject is so immense that it deserves separate treatment. This presentation will concern itself primarily with allergens of simple chemical nature, introduced into the body chiefly orally, by inhalation, and by injection; the manifestations produced by these allergens; and, especially, some of the clinical and investigative problems which emerge from this field.

DRUGS AND MANIFESTATIONS

The manifestations arising from drug allergy are as varied and even more inclusive than those produced by complete antigens such as found in foods, pollen, fungi, and miscellaneous inhalants. An incomplete list includes the following: *Asthma* and *vasomotor rhinitis* may be produced by aspirin, aminopyrine, antipyrin, acetophenetidine, quinine, sulfonechloramides, formaldehyde, and occasionally by penicillin, streptomycin, and the sulfonamides. *Urticaria and angioneurotic edema* may be caused by aspirin, quinine and other antipyretics and analgesics, phenolphthalein, barbiturates, sulfonamides, penicillin, streptomycin, aureomycin, and other antibiotics. *Serum sickness* type of reactions may be induced primarily by sulfonamides, penicillin, and other antibiotics. *Drug rashes* are common and are of various type. Moribilliform eruptions and dermatitides are often produced by barbiturates, sulfonamides, penicillin and other antibiotics, antipyrin, potassium thiocyanate, and also antihistamines.[38] *Fixed drug eruptions* are those which tend to recur in the same locations on the readministration of the drug. They may be due to any of a variety of drugs[1] such as antipyrin, sulfonamides, barbiturates, acetophenetidine, arsenicals, and bromsulphalein.[39] It is possible that such localized allergic inflammation may occur in viscera as well as in the skin, as a result of drug sensitivity or perhaps bacterial or other allergy. *Exfoliative dermatitis,* due to arsphenamines, gold compounds, sulfonamides or penicillin, may be serious in its extent. *Photosensitization* or *erythema nodosum* may occur on occasion. *Contact dermatitis* may be the result of allergy to any of a host of simple chemical substances such as mercury, nickel, cobalt, quinine, dyes, local anesthetics, sulfonamides, penicillin, streptomycin, and antihistamines.

Fever without any apparent other manifestations is most often produced by such drugs as sulfonamides, arsphenamines, thiouracils, and iodides. In cases of *granulocytopenia,* aminopyrine, thiouracil, sulphonamides, arsphenamines, and occasionally antihistamines have been implicated. *Aplastic anemia* has been traced to arsphenamines, sulfonamides, and trimethadione. *Thrombocytopenia* has been caused by quinine, quinidine, sedormid, sulfonamides, and thiouracil. *Polyarteritis* has been caused by sulfonamides on many occasions, and there is growing evidence that similar changes may be produced by penicillin. The association of polyarteritis with sul-

fonamides and the serum sickness type of disease produced by these drugs and serum has been suggested by the experimental and clinical findings of Rich and his associates.[32,33] There is less agreement as to the allergic nature of certain types of hepatitis or neurologic lesions following the use of some drugs. But the possibility of such or other visceral lesions as a phenomenon of allergy to drugs or simple chemicals cannot be dismissed.

Although Mayer[27] and others have attempted to formulate concepts as to the characteristics of chemical substances likely to produce some types of allergy, for the most part we are unable to forecast the likely behavior of any new drug.

It may be useful now to turn to a brief description of the characteristics of the allergenic behavior of two drugs, aspirin and penicillin, each of which may serve as a prototype for large numbers of other drugs.

Aspirin.—Allergy to aspirin has been known for at least half a century. Until sulfonamides became available it was regarded as the cause of the most common form of drug allergy. Storm van Leeuwen[40] of the Netherlands estimated that 10 to 16 per cent of his asthmatic patients were allergic to the drug. Salen[36] of Sweden found 9 to 10 per cent of his asthmatic sufferers sensitive to aspirin. Feinberg[42], Friedlaender and Feinberg,[17] Prickman and Buckstein[13] and Hansen-Pruss[19] reported large groups but found the incidence lower. Gardner and Blanton,[18] on the basis of replies from allergists to a questionnaire, concluded that only two out of every 1,000 allergic patients are sensitive to aspirin. The most common manifestations produced by allergy to aspirin are asthma and urticarial dermatoses, although other allergic phenomena may also occur. The reactions are immediate, and "serum sickness" or delayed type reactions have not been blamed on this drug. The most interesting clinical phenomenon in connection with aspirin allergy is its frequent association with a type of severe, intractable asthma. Most observers agree that the skin test to aspirin is negative in cases of allergy to this drug, although there have been some claims for positive tests with modified procedures.

Penicillin.—Allergic reactions from penicillin by contact have been so numerous that its topical use has been virtually abandoned. Allergic manifestations from internal use of the drug are also common, its claimed incidence varying[20,25,45] but probably constituting around 2 to 5 per cent. It has not been established that the incidence is significantly affected by the route of administration, by the type of penicillin, by the medium in which it is administered, or by the addition of antihistamines. The most common reaction is the delayed "serum sickness" type of syndrome, occurring several days after administration and accompanied commonly by urticaria, angioneurotic edema, arthralgia and swelling of joints, and fever. The incubation period is usually ten days but may be only four or five days or as long as three weeks. The duration of this disease is most often a week

or two, but in some patients the urticaria and angioneurotic edema may last for months. Other forms of allergic response are urticaria, coming on immediately, vesicular eruptions and exfoliative dermatitis, asthma occasionally, and fixed drug eruptions. It has also been suspected that polyarteritis may be produced at times by penicillin. In connection with the vesicular and exfoliative types it has been claimed that they occur most commonly among those who have fungus infections of the skin.

Immediate positive reactions to penicillin are rare. When present, as we found in high titer in one patient, we would anticipate that the therapeutic administration of the drug might result in acute anaphylactic reactions. There is no reason to believe that those persons who have respiratory allergy from airborne mold spores would experience acute systemic reactions from penicillin, since the author has shown several years ago[13] that Penicillium-sensitive patients failed to give a positive skin test to penicillin. The question of delayed skin reactions to tests is more confused, some observers[29,34] claiming that there is a significantly higher incidence of such reactions among those who have had allergic manifestations from penicillin. In contact dermatitis from penicillin the patch test is usually positive. Systemic allergic manifestations from other antibiotics are less frequent.

DIAGNOSIS

Most drugs and simple chemical substances which produce non-contact types of allergic manifestations give negative skin tests. Laboratory reports, frequently encountered, which tell the referring physician that the patient failed to react on skin test to aspirin, sulfonamides, phenobarbital, or similar drugs, are both misleading and dangerous because they may lead the uninformed physician to administer these drugs to patients who are violently allergic to them. It is true that there are some simple chemical compounds which give immediate whealing skin tests in all or in some persons allergic to them. Skin reactions to quinine have been reported.[3,9,28,30] In one of the series, two patients with an asthmatic syndrome gave positive tests, while two others with urticaria only were negative. Phthalic anhydride[14,21] has been shown to give positive tests. Two series of patients with asthma and rhinitis from chloramine-T or halazone with positive skin tests have been reported.[15,35] Occasionally, immediate whealing tests may be obtained with penicillin and perhaps with sulfonamides.

Although most observers feel that a delayed reaction to a skin test with penicillin is not highly diagnostic, others[29,34] are of the opinion that it has some value in forecasting the likelihood of systemic reactions from its administration. In spite of attempts to employ other special procedures, which will be described later, the present status indicates that the skin test is of little use in the case of suspected allergy to most drugs. History and observation are the main criteria by which such diagnoses must usually be made. Occasionally, when the anticipated symptoms are not of a serious nature, cautious administration of small amounts of the drug as a clinical

test may be justified. It should not be forgotten, however, that in the case of some drugs, particularly penicillin, a previous allergic response by no means indicates that the subsequent administration will react similarly.

SOME BASIC CONSIDERATIONS

The Negative Skin Test.—The prevailing explanation for the failure of most drugs and simple chemical compounds to produce a positive skin test is that we are dealing with incomplete or imperfect antigens. This concept has been established by Landsteiner and his school,[22] who were unable to sensitize or shock animals with simple chemical substances unless they were conjugated to proteins or other large molecules. This theory would explain why a drug such as aspirin might produce violent allergic symptoms after combining *in vivo* with body proteins and yet fail to give a positive skin test.

To test this hypothesis we made some preliminary observations a number of years ago.[48] The serum of normal subjects to whom large doses of aspirin were administered failed to produce a specifically positive skin test in aspirin-sensitive persons. Leftwich,[24] in 1944, claimed that in twenty-eight out of thirty sulfonamide-sensitive patients he obtained significantly larger reactions as compared to nonallergic controls, with serum from subjects to whom sulfonamides had been administered. Working with children, Fink and his associates[16] were unable to confirm these findings. Sherman's[37] results were also negative. Mathew and his associates[26] tested twelve aspirin-sensitive subjects with the serum of rheumatic fever patients who had taken aspirin for over three weeks. There was no difference between these tests, the control sera and control subjects. On the other hand, Hansen-Pruss[19] found that the sera from persons who had taken aspirin usually gave positive reactions in aspirin-sensitive individuals. As early as 1929 Coke[6] had made a similar claim. It is my impression that the weight of evidence is against the demonstration of specific positive reactions by this technique. The claimed positive results are probably due to the false reactions usually produced by most serums.

In 1936, Dameshek and Colmes[8] reported that they were able to obtain positive skin tests in three patients having agranulocytosis from aminopyrine by testing them with serum to which aminopyrine had been added *in vitro*. This appeared to open up new diagnostic and theoretical approaches. Blank[2] claimed that addition of aspirin to aspirin-sensitive serum results in an antigen which gives skin reactions in aspirin-sensitive patients. Using both nonallergic serum, allergic serum, and serum from aspirin-sensitive patients a number of years ago[48] and more recently[10] we have been unable to obtain positive results.

In our trials over a period of years we have been unable to find antibodies transferable to man in the serum of patients sensitive to drugs which fail to give a positive skin test. Mathew and his collaborators[26] obtained negative results when skin sites previously injected with serum from

aspirin-sensitive patients were tested with aspirin or serum from subjects who received aspirin. A reversed technique, in which the subjects receiving large doses of aspirin were tested intradermally with the serum of patients sensitive to aspirin, also gave negative findings. Hansen-Pruss[19] succeeded in obtaining a positive passive transfer in one instance. Precipitins or transferable antibodies have not been found in connection with penicillin allergy[37] or most of the other types of drug allergy.

In conformity with the hapten concept of drug allergy in man it would be expected that chemically conjugated drugs would behave as complete antigens, as they do in animals. It was disappointing, therefore, when Wedum[47] obtained negative skin tests in sulfonamide-sensitive patients with sulfonamides diazotized with human serum. No precipitins to the conjugates were found in these patients, nor could the serum transfer sensitivity to guinea pigs. There was no difficulty. however, in producing precipitins or anaphylactic sensitivity in guinea pigs by means of these conjugates.[46] In our laboratory,[11] working with aspirin conjugated with casein or human serum, postive skin tests were not obtainable directly or by passive transfer. However, the serum of aspirin-sensitive patients transferred moderate anaphylactic sensitivity to guinea pigs. Guinea pigs sensitized with the aspirin conjugates gave anaphylactic reactions to the conjugate and also to unconjugated aspirin. Precipitins were obtained in rabbits sensitized to the conjugate. The failure of the conjugates to give a positive skin test in the allergic patient is surprising and may necessitate a revision of our concept of drug allergy in man. One possibility, of course, is that conjugation *in vivo* does not produce the same prosthetic group as synthetic conjugation.

Specificity.—Allergy to simple chemicals may be highly specific, but more often it is group specific. The group specificity may be confined to members of the group having one or another designated characteristic, and this may vary with the individual patient. Only several illustrative examples will be cited. Dawson and Garbade,[9] studying a case of quinine sensitivity by skin testing, found that the patient reacted to several of the levorotatory compounds but not to quinidine and the other dextrorotatory isomers. Similarly, Peshkin and Miller,[30] in a patient with thrombocytopenic purpura due to quinine, obtained a positive skin test with the latter but not to quinidine. On the other hand, in two patients with quinine allergy O'Malley and Richey[28] elicited positive skin tests with quinine but none with cinchonine (dextrorotatory) or cinchonidine (levorotatory).

In clinical allergy to aspirin there is usually no general salicylate sensitivity, if one is to judge by the histories of the patients. In his report in 1919 Cooke[7] stated that in three patients with allergy to aspirin no allergic reactions were obtained with salicylic acid, benzoic acid, antipyrin, methyl salicylate, or sodium acetate. Hansen-Pruss[19] mentions seventeen patients with aspirin allergy and three with allergy to sodium salicylate.

Since the total number of the patients in the report and the number sensitive to particular drugs are equal, it is inferred that none of those who were allergic to aspirin were allergic to sodium salicylate, and vice versa. On the other hand, A. R. Feinberg and Malkiel[11] in our laboratory found that guinea pigs sensitized with aspirin-protein conjugate gave anaphylactic reactions to sodium salicylate as well as to aspirin.

It is well known clinically that the spectrum of allergy to sulfonamides varies from patient to patient. Wedum,[46] approaching this problem several years ago in guinea pigs sensitized with sulfonamide azo-proteins, found that by skin test, anaphylaxis and precipitin test there was an immunological relationship between sulfanilamide, sulfapyridine and sulfathiazole. Langenbach[23] reported four instances of rashes from sodium amytal (isoamylethylbarbituric acid); some of these tolerated luminal (phenylethylbarbituric acid). Feinberg and Watrous[15] showed clinically and by skin test an antigenic relationship between chloramine-T and halazone, but no reactions were obtained with several other chlorinated compounds.

As a whole these findings give the impression that the drug specificity occurring naturally in man is more variable and generally of a narrower range than that produced in animals by artificially induced sensitization with synthetic conjugates. If we could shed light on this difference, it is possible that it would go far toward solving some of the puzzles concerned with drug allergy in man.

It is dubious whether there is a distinct specificity to the different types of penicillin. Much of the opinion that such a difference in antigenicity and specificity exists is based on uncritical clinical observation, such as the ability to tolerate one type after an allergic reaction has resulted from the other. It must never be forgotten that frequently penicillin is tolerated with impunity after a previous "serum sickness" from the same type of drug. In a patient who had two prolonged reactions to penicillin G, both penicillin G and penicillin O gave skin reactions in the same very high titer. Using delayed skin tests as their criterion, Risman and Boyer[34] demonstrated considerable cross reaction between penicillins G, B.T., and O.

Allergy of Unidentified Origin.—We[12,17] and others[31,36] have previously described a class of chronic and severe asthmatic patients who in addition present a history of allergy to aspirin. These patients are characterized by early chronicity, marked severity, early emphysema, marked nasal involvement with polyp formation, and a frequent history of nasal operations. Aspirin will produce extreme allergic attacks, usually asthma, but at times urticaria and other symptoms. The asthma attacks from aspirin are usually severe and have been known to be fatal. In spite of a sputum containing many eosinophils and a frequently high blood eosinophilia, skin tests are frequently negative and when present do not usually explain the chronicity of the asthma. Salicylates in foods, occurring naturally or by addition, do

not explain the chronic asthma in this group, since diets free of foods containing salicylates have failed to produce improvement.[12,48] Some of these patients are also sensitive to other drugs, such as phenacetin, aminopyrine, quinine, et cetera.

If a group of people developed the capacity to become allergic to simple chemical compounds and the range of sensitivity included aspirin, they would be expected to behave exactly as the class of asthma patients described earlier. It is possible that these individuals are allergic to other simple chemicals, such as are found in food, naturally or as additives, or such as are found in the air from combustion of coal and wood or from other sources. It is possible, as Salen[36] has claimed, that the aspirin asthma is an infectious asthma. Although there are some features which speak against this likelihood, such as the eosinophils in the sputum and the usual failure to improve with change of climate, the possibility cannot be altogether denied. It is even possible that infection may result in the production of a simple chemical product responsible for the allergic phenomena. There are also possibilities of intrinsic origin of an allergen other than infection.

If the concept of simple chemical substances as causes of the chronic asthma described above should prove correct, it would probably apply a much larger group of patients than are represented by the aspirin group (about 100 in my practice). In about one third of the chronic asthma patients and about one half of those with vasomotor rhinitis, no allergy or infection can be identified. In the majority of instances of protracted urticaria, allergic causes are either known simple chemicals (aspirin, phenolphthalein, sulfonamides, penicillin) or they cannot be identified. May it not be possible that these also are the types of people who have unfortunately developed an allergy to simple chemicals rather than to proteins? If they take the chemical (drug) from a bottle labelled "aspirin" or "sulfathiazole" and get asthma or hives, they know what they are allergic to, even though these substances will not give a positive skin test. But if they are allergic to just as simple a chemical in the food or in the air, the cause is not identified. Incidentally, it is not beyond the realm of probability that the Penicillium spores in the air or Penicillium mold in foods or even other mold products might be the cause of some obscure cases of allergy comparable to those produced by penicillin administered for therapeutic purposes.

The Augmentor and Inhibitor Concept.—Storm van Leeuwen and Beutner[42] have shown that the blood has an inhibiting action on drugs and that the *in vitro* effects of certain drugs are greater than in the live animal. Storm van Leeuwen showed further[41] that drugs causing allergy are augmentor drugs. If such a drug (aspirin, quinine) were added to the bath fluid in a muscle experiment, it would augment the action of the original drug (pilocarpine). He claimed that all "idiosyncrasy" drugs proved to have this augmentor capacity. He postulated that "allergic reactions" to

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drugs are produced because in allergic people the power of the blood to inhibit the augmentor action is reduced. As support of his theory he claimed[43] that in the patients with aspirin allergy tests showed a reduced combining power of the blood for salicylates. However, A. R. Feinberg and Malkiel[11] have demonstrated that Storm van Leeuwen's technical procedures were in error and that when proper precautions in technique are used, the blood of aspirin-sensitive patients does not show a reduced capacity to combine with salicylates.

SUMMARY

In this presentation I have attempted to point out the importance of the subject of drug allergy. It is important because of the increasing array of drugs at our disposal which has widened the scope and incidence of drug sensitivity. It is perhaps even more important because the characteristics of allergy to such simple chemicals point to a clue to a possible group of unidentified chemicals as a cause of allergic manifestations, whose etiology is unknown at present. Restrictions of time and space have compelled the omission of many important phases of this subject, such as possible specific treatment, the possible explanation for the negative skin test with conjugates, contact dermatitis, and others. It is my hope that this shortened version of an immense subject will have stimulated some of you to give it thought and a few of you to set the thoughts in motion toward serious investigation in this field.

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A STUDY IN THE PATHOGENESIS AND CLASSIFICATION OF DERMATOLOGIC PENICILLIN REACTIONS

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DERMATOLOGIC reactions following penicillin therapy are fairly common. Many articles have been written describing various forms of reactions to this drug, and most of us have been confronted with some of them in our own personal practices. Yet in a study of the literature very little investigation of the mechanism or the pathogenesis of the reactions has been reported, and there have been few attempts to organize or to classify them. I feel that such a commonly encountered complication of present-day therapy should be studied to see if some pattern attends these reactions, with a view to preventing or treating future cases.

In general, summaries of penicillin reactions resemble that of Long,[11] who stated that toxic penicillin reactions consist of drug fever, dermatitis, urticaria, asthma, and anaphylactic shock. No statement of any pathogenic mechanism is made except that previous fungous infections may sensitize to penicillin. The basic explanation of this postulate probably is found in the studies of Jadassohn[8] in 1937, which showed that fungi contain both a specific and nonspecific antigen. Thus an individual can be sensitized to one specific type of fungus, or by one type of fungus can be sensitized to many types through the common, nonspecific antigen. In view of the fact that fungi doubtless grow on the skin of all individuals, this probably is the explanation for reactions in persons never before having received penicillin.

The early reports of penicillin toxicity mentioned only urticarial types of reactions. Keefer[9] in 1943 reported only 2 per cent urticarias, and Stokes[16] reviewed about 1,000 cases in 1944 with only slightly over 2 per cent urticarias. Graves[4] in 1944 had two cases of pompholyx occurring after penicillin therapy, and Downing[1] in 1945 reported a case of bullous dermatitis following administration of the antibiotic. In the same year Lamb[10] reported two cases with erythemato-vesicular eruptions on the hands and in the groin. Also in 1945 Rostenberg estimated that penicillin reactions, besides increasing in variety, had increased in frequency up to 5 per cent in his 144 cases. By 1950 Long[11] felt that this figure had risen to 10 to 15 per cent. Thus, as more patients are being exposed to penicillin, the reaction rate is rapidly growing, and the problem is increasing into one of major importance.

In 1944 Sulzberger[17] proposed three possible mechanisms to explain the pathogenesis of the toxic reactions to antibiotics:

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1. A Jarish-Herxheimer type of reaction in which the killed organisms liberate substances that cause the toxic changes.

2. A synergistic or additive effect of penicillin plus a dormant etiologic factor which acting together bring the response seen.

3. An allergy to penicillin, general or local.

Since this report, all papers dealing with the problem of pathogenesis of antibiotic toxicity have followed one, two, or all three of these proposed mechanisms. I believe this scope must be somewhat enlarged.

The several papers dealing with penicillin reactions have either simply listed the various types of reactions seen, or grouped them by the dermatologic form the reaction has assumed. For example, Newman[12] in 1947 listed the following reactions: (1) urticaria, (2) miliaria, (3) erythema nodosum, (4) purpura, and (5) erythematous papulovesicular eruptions. Templeton[18] in the same year groups them as follows:

1. Epidermal reactions—by contact with penicillin.
2. Dermal reactions—parenteral exposure.
   (A) Urticarial. (B) Phytid type.

I feel that a little more can be learned by enlarging on Sulzberger's list of mechanisms and then grouping the various reactions by pathogenesis.

ILLUSTRATIVE CASE HISTORIES

Case 1.—A middle-aged white man was treated for a recurrent tracheobronchitis by inhalation of 100,000 units of penicillin daily for eight days. On the eleventh day after the onset of therapy, the patient developed a severe generalized urticaria, including the hands and feet. There was no evidence of any eczematous eruption or pompholyx at any time. There was a mild albuminuria on one occasion. The blood count was normal and the blood serology was negative. With soothing baths, sedation, antihistamines, and adrenaline, the patient recovered, and to date there has been no recurrence.

Case 2.—A middle-aged white man who had never before had penicillin but did give a history of athlete's foot previously on several occasions was given one injection of repository penicillin, 300,000 units, as prophylaxis following suturing of a laceration on his leg. On the second day after the injection his hands and feet became swollen and pruritic. The next day his hands and feet showed deep intraepithelial vesicles typical of pompholyx. Some of these ruptured, some resolved in the next few days. Also on the second day an erythematous papulovesicular eruption was seen in both groins which in the next two weeks began to exfoliate. On the eleventh day following penicillin therapy, he developed a generalized urticaria which required hospitalization.

Case 3.—A young white man with no history of previous penicillin was hospitalized for cough and fever. Four days before admission he had been given depot penicillin, 300,000 units. On the second day after the injection his hands and feet began to itch, and an erythematous papular eruption appeared in the groin. On admission he presented a bright red maculopapular rash over all flexural areas of the body, becoming confluent in both groins. Deep vesicles of the pompholyx variety were seen on palms and lateral borders of his fingers. A mucopurulent nasal discharge with bilateral cervical lymphadenopathy was seen, and scattered moist râles were

heard throughout both lung fields. Sinus x-rays showed clouding of all sinuses. On sulfa drugs the chest cleared, the temperature returned to normal, and nose and throat symptoms disappeared. The groin and axillae became vesicular, then dried and exfoliated. The palms went through a mild picture of dyshidrotic eczema without secondary infection, then dried, exfoliated, and healed.

Case 4.—A fifty-five-year-old white man was given penicillin prophylactically after herniorrhaphy, 400,000 units, repository type, daily. On the third day of penicillin therapy an eczematous, red pruritic rash appeared in the groin and on the scrotum. This rapidly became vesicular and then oozing. The hands and feet remained clear. There was no history of previous penicillin therapy, but he did have a severe oozing dermatitis of the groin several years ago which was diagnosed as "jockey itch." With sedation, permanganate washes, fungicidal creams, and antihistamines the areas gradually dried, exfoliated, and healed. Two months after healing, intradermal tests to penicillin and Trichophyton were done. The patient was negative to penicillin, but there was a moderately positive delayed reaction to Trichophyton.

Case 5.—A young white woman of Italian extraction with dark, oily skin had had occasional sieges of dandruff and "itchy scalp," controlled by frequent shampoos. She was admitted to the hospital for an upper respiratory infection and given four days' repository penicillin. Two and one-half weeks after discharge she came to my office with severe, acute dermatitis of the scalp, nasolabial folds, neck, and post-auricular areas, and a mild pompholyx type of eruption of both hands. A diagnosis was made of acute seborrheic dermatitis with "seborrhid" of the hands. The areas slowly cleared with Burow's soaks, local antiseptic and keratolytic creams, and x-ray therapy.

DISCUSSION

With the help of the cases cited and illustrative cases from the literature, I should like to attempt to organize the types of dermatologic reactions to penicillin from the standpoint of their pathogenesis. A skeletal outline is suggested here:

Group A: Epidermal contact reactions with localized dermatitis and sensitization restricted to areas of application.

Group B: Dermal reactions regardless of the route of administration, whether by local application, by ingestion, by inhalation, or by injection.

Type I: Specific penicillin reactions.

Type II: Reactions to the vehicle, the base, or the culture medium upon which the penicillin was grown.

Type III: Nonspecific reactions to the common mold antigen.

Type IV: Jarish-Herxheimer reactions of the bacterid type from liberation of toxins from organisms killed by the penicillin.

Type V: Reactions from a disturbance of the "symbiotic balance" of organisms growing on the skin surfaces.

Epidermal Contact Reactions.—This type of reaction scarcely needs discussion, as it has been seen by all of us after using antibiotic creams locally. One question previously raised by Epstein[2] in 1946 should again be brought to attention. Is it possible to sensitize but one area of skin by local contact with penicillin? An eruption that involves the epidermis alone is not necessarily true contact eczematous dermatitis. Also, external

contact may well cause a generalized dermal sensitization. If we have reactions following antibiotic contact that seem to remain local, it may be a matter of degree only.

Templeton[18] described a man treated with penicillin solution locally for a dermatitis of the beard. On the second day of the treatment there was a flare of the dermatitis, and the penicillin was discontinued. The dermatitis was cleared by other local therapy, and a week later a patch test was done with penicillin. This was positive, which allegedly shows an epidermal sensitization. Two months later the patient was given intramuscular penicillin for a dental infection. In twelve hours the entire dermatitis of the beard had recurred, and three days later the patient suffered a severe generalized urticaria. As there was no previous and no intercurrent use of penicillin, it is assumed that the dermal sensitivity came about through the epidermal contact with the drug. Therefore, because of the high index of sensitization as well as the possibility of inducing generalized dermal sensitization, I can only condemn the local use of this antibiotic.

Dermal Reactions Specific to Penicillin.—It is entirely possible that the urticarial reaction is the only dermal reaction specific to penicillin. It is a delayed reaction, coming on seven to twenty-one days after the first administration of the drug, and apparently is induced by treatment. The period of delay is the incubation period, and this may be shortened as an accelerated reaction seen in cases receiving a second or third exposure to penicillin. Peck[13] found that all patients who had no urticarial reaction to penicillin gave negative skin tests; however, the skin test was not uniformly positive in urticarial cases. He stated that sensitivity is often temporary and that penicillin may often be tolerated later.

This is the reaction that may be prevented by the use of penicillin O. In Volini's[19] original article, reporting on 152 cases, all cases of dermal reactions to penicillin G (benzylpenicillin) were of the urticarial or serum sickness type except one described as a papulovesicular exanthem. One point should be made clear with Volini's work and others dealing with the "less-allergic penicillins." They report that only 10 per cent of patients who react to penicillin G also react to penicillin O. However, we find this same 10 per cent figure of urticarial reactions to penicillin G with the general public, so that the low percentage of reactors to penicillin O that they report may be only the expected statistical figures of individuals sensitive to each and both of two drugs.

Reactions to the Vehicle.—These reactions are difficult to separate from those due to the penicillin itself, for most patients in the literature (and all in this report) were not tested to the vehicle, the base, the culture medium used to grow the penicillin, nor to other brands of penicillin.

A case cited by Goldman[3] in his 1946 report was that of an exfoliative

dermatitis following penicillin injections. Patch tests done later were postive only to the specific brand of penicillin used, and negative to all other brands.

It is conceivable that this may explain some of the success found with penicillin O and other penicillin salts. However, much work must be done yet to evaluate these less allergenic penicillins, especially concerning their alleged ability to desensitize to penicillin G.

Nonspecific Reactions to the Common Mold Antigen.—This, I believe, is the mechanism of most of the immediate eczematous, bullous, pompholyx, or vesicular eruptions described. The eczematous eruption in the groin described in Cases 2, 3 and 4 is frequently encountered now in the literature and in all cases seems to be associated more with the pompholyx reaction in time of appearance, in history of previous fungous infection, and in having a positive Trichophyton test, as illustrated in Case 4.

Cases cited by Graves[4] and Goldman[3] showed positive Trichophyton tests and negative penicillin tests, while those eczematous reactors described by Peck[13] showed consistently positive reactions to both Trichophyton and penicillin. The Trichophyton test in this type of reaction seems to be the more reliable. Patch tests for dermal reactions to all medications, as reported all through the literature, are inconclusive, and Peck[13] with a series of 500 cases decided that the patch test was entirely unreliable for evaluating penicillin dermal sensitivities.

Two cases are cited by Samitz and Horvath[15] that are instructive. The first was a forty-year-old man with a chronic recurrent eruption of the scrotum and crural areas. He was given two injections of penicillin, and three days later suffered a severe, generalized eczematous eruption. Patch tests to penicillin were negative. The second was a twenty-nine-year-old woman with a chronic follicular eruption on the scalp. Twelve hours after ingestion of penicillin tablets she developed a severe generalized eczema.

Huber[6] reported an exfoliative dermatitis following penicillin in a patient with a chronic epidermophyte infection about the feet of several years' duration. Twelve hours after the injection of the drug a generalized papulo-pustular eruption appeared, and on the sixth day the skin over the entire body exfoliated. Skin tests to penicillin were negative and to Trichophyton positive.

In the cases of the erythematous eczematous eruptions in the groin, it is likely that we are dealing not with an "allergy" to penicillin but rather with a dermal sensitivity to the common mold antigen induced by previous fungous infection. This fungous infection may be active or dormant, or conceivably entirely eradicated, but the dermis locally or generally maintains its sensitivity. When the penicillin is introduced into the system, the common-antigen sensitivity is sufficient to precipitate an eczematous dermatitis.

Similarly, in the cases of fungous infection of the feet that flare up

following penicillin, it is likely that many of them are again eczematous eruptions primarily induced by the common mold antigen sensitivity. Also, the pompholyx or "id" reactions are likely local sensitization responses in the dermis of the palms or soles to the presence of the common mold antigen. Ingraham and Beerman[7] in their discussion of dermato-allergy suggest a possible mechanism for this occurrence of pompholyx on hands and feet. They postulate that since pompholyx is a dermal reaction in which the allergen is distributed through the blood stream and the response is predominantly vascular, and since the hands and feet are dependent areas subject to vascular stasis, the stasis may allow localization of the tissue reactions in the palms and soles.

In none of these cases are there necessarily any demonstrable circulating antibodies to penicillin, although there may be, and these account for the later urticarial type of reaction in the same patient as we reported in Case 2. Thus, with no actual "penicillin allergy," skin tests to penicillin may be negative, and still injections of penicillin produce pompholyx, eczematous eruptions in the groin, or in an apparent flare-up of existing fungous infections.

The practical point to be derived from this discussion is that some of this type of reactions can be prevented. All patients getting penicillin should be asked not only if they have had penicillin before and with what effect, but also if they have had previous fungous infections (in words they understand). In the presence of a history of a skin eruption that may have been fungous, especially if chronic or prolonged, in a patient with whom penicillin therapy is essential, the physician should at least begin potassium permanganate washes to the suspicious areas along with the antibiotic therapy and watch for the beginnings of dermal reactions.

The Jarish-Herxheimer Reactions.—These dermal reactions that follow penicillin therapy are not due to penicillin sensitivity nor to sensitivity to the common mold antigen. Rather, these depend upon a sensitivity to the products of decomposition of bacteria or fungi. Also, the bacteria or fungi that liberate the products must be nonresistant to penicillin, thus flooding the system with disintegration-toxins liberated when they are killed by the injected penicillin. In view of our present-day concepts that many of the chronic eczematous dermatoses are caused by various forms of bacterial hypersensitivities, it is vital to recognize toxic penicillin reactions.

Heinlein[5] reported several cases of chronic eczema aggravated by penicillin. He attributed this to the Herxheimer type of reaction in skin sensitized to bacterial products over the long period of duration of the eczema. Templeton[18] also found similar flaring of existing eczema when penicillin was administered. Lamb[10] discussed the administration of penicillin to a patient suffering from actinomycosis of the jaw. On the fifth day of treatment a pompholyx eruption appeared on the hands and an eczematous

eruption in the groin. Skin tests to Trichophyton and penicillin were negative, but were positive to Monilia. Lamb felt that the eruptions in this case were due to the liberation of toxins from the penicillin-sensitive actinomycosis organisms acting as a Herxheimer reaction on areas of the body previously sensitized to Monilia, although no history of such infection was given.

Probably, in view of the much higher percentage of penicillin reactions in patients with long-standing dermatoses, and in view of the greater possibility of inducing a Jarish-Herxheimer type of reaction, penicillin should not be freely administered to them.

Symbiotic Imbalance.—In all likelihood the most insidious type of toxic reaction to penicillin is this effect of altering the balance of organisms present on the body surface. The normal skin harbors millions of parasitic and saprophytic organisms competing with one another for the available food supply. The interrelationships of these various types of organisms must be very complex, one type suppressing the growth of other types, and conceivably aiding in the growth of still other types. When a powerful antibiotic such as penicillin is suddenly added to the system, susceptible organisms die and the nonsusceptible increase in numbers. Often, we are now finding, these penicillin-resistant organisms, growing without normal competition from the other organisms, are becoming pathogenic and extremely troublesome to treat. More and more by the use of penicillin we are increasing the number of the penicillin-resistant infections, and this is true not only on the skin, but in the ear, nose, throat, chest, bowel, and urinary tract. Many cases such as Case 5 are being seen by all of us, and similarly there are increases in the number of intertrigo, monilial types of pruritus ani, and infections due to pyocyaneus and Proteus. Case 4, listed as a Jarish-Herxheimer type of reaction, certainly could be described as a reaction caused by a disturbance of the symbiotic balance, but there is no proof of any latent activity in the groin persisting in this case over the many years from the original infection until the flareup following penicillin. At any rate, many cases listed as allergic eczematous eruptions, id eruptions, or flares of fungal infections may be ultimately traced to such imbalances of skin organisms brought about by the sudden presence of penicillin.

Woods[20] reported many cases of sore mouth, hairy tongue, thrush, and perleche from the use of antibiotics locally in the oropharynx. Also he described a few cases of diarrhea with Monilia in the stool following the use of penicillin, and two cases of bronchopulmonary moniliasis after antibiotic therapy. *In vitro* studies on mixed cultures showed that penicillin had no effect on the growth of monilial organisms.

This type of antibiotic reaction, I feel, is growing rapidly in importance and warns all of us in the use of any of the antibiotics. As our knowledge of the etiology and involvement of bacteria in skin disease increases, our understanding of these symbiotic relations will increase. Certainly it warrants further investigation.

SUMMARY

Dermatologic reactions to penicillin have increased in frequency from 2 per cent, reported in 1943 by Keefer, to 15 per cent, reported by Perrin Long in 1950. Many types of reactions have been recorded including urticaria, pompholyx, vesicular eruptions, bullous dermatitis, miliaria, purpura, and flaring of existing dermatoses.

Five cases from the records of Sharon General Hospital are reported illustrating various types of penicillin reactions.

An attempt was made to outline and organize the types of penicillin reactions from the standpoint of the pathogeneses:

Group A.—Epidermal contact reactions with localized dermatitis, and with sensitizations restricted to areas of application.

Group B.—Dermal reactions, regardless of the route of administration.

1. Specific penicillin reactions limited to urticaria, a delayed reaction coming seven to twenty days after drug administration.

2. Reactions to the vehicle, the base, or the culture medium used to grow the penicillin.

3. Nonspecific reactions to the common mold antigen described by Jadassohn. The Trichophyton intradermal test is believed to be the most reliable to determine this sensitivity. Patients receiving penicillin who have a past history of fungus infection should have fungicidal preventive therapy started along with their penicillin.

4. Jarish-Herxheimer reactions to disintegration-toxins liberated from organisms killed by the penicillin therapy. Patients with chronic eczematous dermatoses probably should not have penicillin unless absolutely necessary.

5. Reactions caused by a disturbance of the "symbiotic balance" of skin organisms by the presence of penicillin. It is hoped that future investigations will deal with skin organisms and their interrelationships.

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MECHANISMS OF PENICILLIN REACTION

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A CERTAIN calculated risk is involved in the clinical use of any drug. In recent years several drugs have been released by ethical pharmaceutical houses only to be withdrawn in haste as reaction incidence mounted during the trial period which every drug must undergo. In spite of all precautions and conservatism, it must necessarily follow that a high latent sensitization potential of a new drug can be made known only by time and usage. Penicillin is no exception in this respect.

The large-scale production of hypoallergenic penicillins bears witness to a higher reaction incidence to the older preparations than the public or the medical profession will tolerate without comment. The comments on the subject by the doctor and the recipient vary widely. The profession accuses itself of sensitizing the public in promiscuous use of the drug. In deference to the profession, it may be said that penicillin has been tried on everything, and justly so. After all, the first crude penicillin, issued in 1942, opened a highroad of new medical procedure that later became known as antibiotic therapy. The usage of this medium without restraint was bound to follow, due not only to the enthusiasm of the doctor but also to the insistence of the patient.

These modifications of the original penicillin mentioned earlier were preceded by other moves to anticipate penicillin reaction. Simon[7] reported, in 1950, at the Sixth Annual Congress of the American College of Allergists, on his experience with penicillin plus Decapryn® and other antihistamines given to known penicillin reactors with minimal reaction incidence. But are these hypoallergenic maneuvers and modifications necessary? Time will answer that question as well as whether they are actually hypoallergenic.

If the medical profession is entirely responsible for sensitization of the public, how can we explain the reactions of those who have never before been given medicinal penicillin? Reactions occurred in 1942 and 1943 in individuals who could not possibly have received previous injections of the drug. In his review of this subject, Brown[1] has reported penicillin reactions occurring as early as 1943. The original reactions were blamed on impurities in the first editions of the drug, which ranged in color from brown to amber in solution. The fact remains that we saw penicillin reactions early and ergo in individuals who could not have been so treated on previous occasion or so sensitized by earlier injection. There was no commercial penicillin before late 1942. We will have to look elsewhere to explain the reactions in these neophytes.

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The argument that the incidence of penicillin reaction is high is not borne out statistically. Rhodes[5] reports an incidence of 3 to 4 per cent; Long[4] an incidence of 5 per cent. If tetanus antitoxin were given as often as penicillin, the incidence of foreign protein reaction would be much more of a problem. In spite of alarm over the present status of penicillin usage and the evaluation of processed hypoallergenic varieties, the original drug still remains the antibiotic of commonest resort in medical practice. Although we have been accused of sensitizing the public, of creating penicillin-resistant strains of bacteria, and of promiscuous laxity in using the drug, there remains much to be explained that will absolve the profession from sole responsibility. The clinical evaluation of penicillin is still far from complete, but some perspective concerning its present status is possible and in order now.

We will have to look elsewhere for mechanisms of penicillin sensitization which are not man-made by the physician. How else can we explain the initial reactions in the unsensitized, the prolongation of symptoms, the relapse and the persistent dermographism after therapy has been expended? The answer may lie *in a mechanism of continuity.* Antigenic material may be harbored in the corpus of the individual or in the effluvia of his environment. There are many such mechanisms possible, some presumptive and some proved. It must be remembered that our commercial penicillins are derived from a common mold which is known to be antigenic, which may become pathogenic, and which is widely distributed in nature. It is also a windborne inhalant antigen.

MECHANISMS OF SENSITIZATION

1. *Transfer and Sensitization in Utero.*—It has been demonstrated that penicillin passes the placental barrier and may be found in a ratio of two-thirds of the maternal circulation in the fetal blood. We must bear in mind that it is fairly common for an infant to have clinical symptoms of allergy, including hay fever and asthma, shortly after birth. The sensitizing mechanism must occur *in utero,* following transfer of antigenic material from maternal to fetal circulation, in order to explain acute symptoms seen so early in life. Preliminary sensitization must occur in order for the newborn to react to an antigen in the outside world shortly after birth.

2. *Antigen-Antibody Reaction.*—The antigen-antibody reaction undoubtedly occurs and may also be proved. Although the penicillin molecule has an amino-acid-like structure, it has been shown to be antigenic on direct testing and by passive transfer. However, this obvious type of reaction will account for only a small percentage of the whole. Penicillin reactions are also frequently seen in nonallergic individuals.

3. *Hapten Formation.*—Penicillin may also act as a hapten in combination with serum protein as a sensitizing agent. It has been shown by

Chow and McKee[2] that such a combination of penicillin and serum albumen, producing a penicillin-protein complex, does occur. This will account for a great many more reactions than the preceding type. It will especially serve to explain the large number of cases of penicillin reaction in individuals who are nonallergic and in whom no allergic mechanism can be demonstrated by the usual means.

4. *Common Antigen Effect.*—Common antigen effect may explain the occurrence of some reactions. Human mycoses, especially tinea pedis, capitis, crurae, et cetera, may predispose to reaction by common protein effect. This may be demonstrated both experimentally and clinically. Sulzberger and Baer[8] have found an antigenic relationship of penicillin to other fungi and have reported that Trichophyton and perhaps other pathogenic fungi have an antigen in common with penicillin. This may account for the vesicular reactions resembling fungus disease which may be seen on the hands, on the feet, and elsewhere following penicillin administration. This common antigenic substance, a byproduct of the growth of a parasite in the human skin, may therefore be a predisposing factor in some penicillin reactions.

5. *Inhalant Antigen Effect.*—The mechanism of action of inhalants may be postulated. Penicillium mold is a common contaminant of walls, bedding, leathers, and vegetation. A sensitive individual may live in such a contaminated environment and inhale its spores. Many of the mold group, including the Penicillia, are known to be responsible for airborne inhalant allergy. Penicillium sensitization may be proven clinically by both direct testing and passive transfer. Cooke[3] considers Alternaria the most common mold allergen, but Penicillium is ranked second in importance in this category. The inhalation of the spores and mycelia of this organism may presensitize the individual so exposed before any therapy with medicinal penicillin derived from this parent source.

6. *Ingestant Presensitization.*—In a similar manner, we cannot overlook the fact that Penicillium growths may be ingested and sensitize the individual in the form of a food allergy. For example, a number of imported and domestic cheeses are deliberately planted with Penicillium of several species, which accounts for their characteristic appearance and flavor. Among these are the Roquefort, Camembert and Gorgonzola varieties, all of which contain some species of Penicillium. It is conceivable that the casual or frequent ingestion of such deliberately contaminated foods may predispose to reaction. In a similar manner, it is possible for chance contamination of a staple food by Penicillium growth (a common bread contaminant) to be a forerunner of sensitization. Since all techniques of penicillin administration, whether by injection, ingestion, or aerosol inhala-

tion, may be followed by a general reaction, we have presumptive evidence that these portals of entry may initiate preliminary sensitization when so implanted with viable mold.

7. *Penicilliosis.*—This is another interesting possibility. There is evidence confirming this as a factor. Sanchez-Cuenca[6] based this finding on a small number of cases, but evidence has been presented that the presence of the mold in pathogenic form in lung abscess may predispose to sensitization to penicillin administration itself. Penicillia are frequently recovered from the feces in routine stool examinations. The presence of this organism as a saprophyte in the bowel may predispose to reaction in a similar manner.

SUMMARY AND DISCUSSION

Penicillin is one of the most indispensable drugs. It is still more widely used than all other antibiotics combined. Incidence of reaction to penicillin may have caused alarm in some segments of the medical profession but not all. Incidence of reaction may be on the increase, but it is also true that reaction syndromes are more readily diagnosed at the present time because we are more aware of this possibility. An undetermined but substantial number of reactions occur in individuals unsensitized by previous injection.

CONCLUSIONS

1. Seven possible mechanisms of presensitization to medicinal penicillin have been described.

2. Several portals of entry have been mentioned through which Penicillium mold may gain entrance as a saprophyte or pathogen.

3. The evidence described is presumptive in some arguments but may be proved in others by common laboratory procedure.

4. Penicillia are widely found in nature and may perpetuate a mechanism of continuity.

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995 Madison Avenue

REGIONAL FACTORS IN ALLERGY

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ENVIRONMENTAL factors, as is well known, affect the incidence, frequency, and severity of allergic diseases. One must include among environmental factors such regional conditions as geography, climate, and local air contaminants. While the mechanisms and manifestations of allergy are identical the world over, the regional factors naturally vary. It would, therefore, seem desirable and informative to collect the pertinent data. This is but a pilot study. Other such studies are being made and will no doubt serve a very useful purpose. Allergic patients frequently request such information when planning to travel. In some instances patients seek advice regarding a change in residence in the hope that it may improve their condition. This paper will deal with a summary of our knowledge of the following factors: geography, climate, with particular reference to temperature and moisture (fog, humidity, rain and wind), and air contaminants (source, method of disposal, mineral, and flora such as pollens and molds).

GEOGRAPHY

What are the geographic factors which influence our climate and therefore affect allergic symptoms? The area referred to in this paper includes Western Pennsylvania and the adjacent portions of West Virginia and part of Ohio, with Pittsburgh as a center. This area embraces the heavy industrial region of the Ohio River Valley and is located in a major storm belt. There are ten storm tracts that traverse the United States, and seven of these are close enough to the Pittsburgh district to affect its weather. This, coupled with the presence of a rough and broken terrain, contributes to air turbulence and wind formation. Furthermore, the location of the rivers adds to the humidity and dampness of the region, affecting vegetation, mold formation, and respiratory disorders. These rivers follow a generally westerly course and meet at Pittsburgh as the apex of a large triangle. They form the Ohio river which goes northwestwardly for a way, then turns sharply south to meet the Mississippi. Winds coming from the northwest have a tendency to wash the grit of the Ohio river valley industries over the Pittsburgh area.

CLIMATE

In general, the climate is temperate; however, the proximity of this zone to the storm tracts already referred to produces labile weather conditions.

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The storms bring low barometric pressures, followed characteristically by high pressures, clear skies, and low temperatures. In spite of this, the climate is truly moderate, as indicated by the fact that there are about 100 days during the year with temperatures below the freezing point, but temperatures below zero are rare. At the same time there are only sixteen days a year with temperatures at or above 90° F. It therefore follows that although there are a considerable number of cold days and a few very warm days, extremes in either direction are not common. January is the coldest month with a mean of 31° F, and July is the warmest at 74° F. This is about the same as Philadelphia but warmer than Boston and Chicago. The average yearly temperature is 53° F with a range from a low of 44° F to a high of 62° F. On the other hand, there is a mean daily temperature of 20°F, and variations of 30° to 35° do occur. These figures do not set the district apart from other areas of the country. For instance, Florida and Arizona have greater variations from day to day. Drops in temperature of 50° are not rare in Tucson, Arizona. As a matter of civic pride, and in order to refute existing impressions, it is well to point out that the sun is out about 50 per cent of the possible time. This misconception concerning the degree of sun-screening in this area may be refuted by the experience of one of our patients, a nurse, who had sunlight allergy. She changed positions to come to Pittsburgh in the hope that she would have fewer symptoms as a result of minimal exposure to sunlight. Subsequent experience proved otherwise. Two-thirds of our days are relatively cloudless. As far as rain is concerned, two-thirds of our days are rain free, and the wet third includes about thirty-five snowy days. There are several inches less rain here than in New York, for example. Prevailing winds are from the northwest and, in general, are about six miles an hour, although forty-mile-an-hour winds are not uncommon.

Yearly averages of humidity in this area approximate 75 per cent in the early morning and 60 per cent during the day. These are not unusual levels and are compatible with comfort. In general, high levels of humidity make extremes of cold and heat unbearable. Parenthetically, it may be stated that conditions of humidity, while not optimal, compare not too unfavorably with those found in many parts of the country reputed to be beneficial for patients suffering from respiratory disease.

CONTAMINANTS

Superimposed on the influence of climate is the influence of particulate contaminants of this area. These include industrial irritants, dusts of all kinds, pollens, and molds. The industrial range includes the preparation and fabrication of steel and iron, glass, foods, chemicals, papers, paints, tars, plastics, soaps, as well as pursuits such as quarrying and mining. To this should be added factors usually found in other busy industrial centers: namely, traffic, with the resultant combustion of fuel; building and high-

way construction; and soot, ash, tars, and sulfur from combustion of coal. In connection with the latter it should be pointed out that smoke-control legislation has been enacted in Pittsburgh and has brought about a significant amelioration of conditions although by no means complete solution of the smoke problem.

Air contaminants are removed by snow and rain through washing and also by air movements. These latter may be in the nature of winds which clear the air in the horizontal plane, or they may be in the nature of convection currents which carry the contaminants upward. These currents are dependent on relative differences between the temperature of the earth and that of the air. As a result of these currents, there occurs an upward dispersal of low-lying contaminants. Exact objective data with reference to this factor, especially from a comparative point of view, is not available. It would appear, however, that we have many periods in this area when optimum conditions of dispersal do not exist. When they do occur, they last but a short time. In one instance in the recent past, a period of inversion which lasted for a considerable time resulted in the well-publicized Donora disaster, which had its effect principally on patients with pulmonary disease. Their symptoms resulted from the inhalation of air contaminants which were not removed effectively. Fogs are also the result of such inversion factors and occur when the moisture in the air is at or near the saturation level and is not removed by either wind, upward dispersion, or precipitation. There are twenty-five to thirty dense fogs a year, but these are generally dissipated by 10:00 o'clock in the morning. The part of the year in which such conditions prevail is for the most part during the wet months of June, July, August, and September. Fogs occur much more often in the West Virginia zone than in the rest of the area.

For the purpose of this paper we shall omit a discussion of the prevalence of pollens and molds. Suffice it to say that the pollinating period is from February to October. The nature and concentration of pollen may be found in the many reports that deal with the subject. Molds are found perennially in houses for the most part. Seasonal molds are widely distributed according to conditions which prevail for the entire Eastern seaboard. Accordingly, allergic diseases caused by pollen and molds are found here with the same frequency as in the midwestern and Eastern communities.

DISCUSSION

There is considerable evidence in the literature to indicate the profound effect that climatic conditions and air contaminants have upon health and disease. The question that interests us specifically here is in what manner these factors affect allergic disorders as they are found in the Pittsburgh area. In order to answer this question it would be necessary to say something about the physiologic mechanism of allergy, with special reference to

the manner and extent to which it is affected by weather or by nonspecific air contaminants. The allergic response is related largely to the function of the capillary bed, especially in manifestations of superficial structures such as the nasal and bronchial mucous membranes and the skin. It is easy to see then that changes in barometric pressure will exercise some influence on the calibre of the capillaries, and hence on capillary permeability. Such changes in barometric pressure are associated with stormy situations and aggravate allergic conditions. Turbulence at these times stirs up the air and brings about an increase of air contamination. Subsequently as the winds or rains develop, there occurs clearing of the air. Another factor which may possibly influence symptoms is the psychosomatic response to stormy weather. It is probably for these reasons that just before storms, patients with respiratory allergy are worse, only to find that their condition improves after the rain washes the air free of irritants.

The response of patients suffering with respiratory allergy to the temperature conditions in this area are varied but on the whole are quite good. The greatest effect is noticeable when there are marked variations in the temperature. In general, our patients are better in the summer than in the winter, provided they are not sensitive to pollen. Factors other than temperature contribute, however, to this end result. Specifically, these are the prevalence of respiratory infections in the winter, and exposure to fumes, gas heat, and indoor dusts because of confinement to the house. It is also possible that the capillaries of the mucous membranes of the nose and bronchi dilate in a physiologic manner in an attempt to warm the cold inspired air. Nasal stuffiness and other nasal and bronchial symptoms may result. Allergic skin disorders, however, tend to be worse during the summer. The exact reason for this is not obvious, but it may be due to increased sweating and vascularity as well as maceration.

Increased humidity and fog influence respiratory allergy adversely, probably because of the increased breathing resistance produced by the particles of moisture in the air. Furthermore, the conditions which lead to the accumulation of fog also produce high concentrations of particulate contaminants. Exposure to nonspecific irritant fumes also aggravates or precipitates allergic symptoms for obvious reasons. These are local factors. Asthmatic patients living near slag dumps or factories which produce acrid or pungent odors will often improve by moving a few miles away. It is a fact, however, that smog, fog, dust, and other contaminants are bothersome in this region. Pollen and molds as causes of allergy operate in a manner analogous to their manner of operation elsewhere. Hence, no special discussion is needed in this connection. We do not know of any pollen or mold free places in this region — those that are reputed to be pollen free resorts have gained this reputation largely as a result of effective although misleading publicity.

One may conclude that there is no optimum weather pattern for all

allergic conditions. Each allergic disorder and each allergic individual has special needs and the weather conditions best suited to his needs must be individualized. To generalize, recognizing the limitations stated, modulation in all elements of environment would probably afford the greatest comfort to the greatest number. The weather in this area tends to be somewhat colder than desirable and has a fairly significant daily variation in temperature. Humidity levels tend to be high but are not striking in any direction. There are few prolonged periods of stability but their potentiality of developing is limited. Industrial contamination of air is still marked but steadily improving. Suburban and rural areas to the north of the city are relatively clean. Before considering climatotherapy for any patient, an initial effort should be made to control the various complications of the allergic state such as infection, pulmonary emphysema, and fibrosis. These factors are often neither recognized nor treated. Lack of proper care in this respect dooms the allergic patient to continued illness. Climatotherapy will likewise fail under such circumstances. Very commonly, however, patients are referred to "spa areas," often after only half-hearted or negligible allergic study and care. Even worse, patients with a difficult and refractory asthmatic condition are encouraged to "change climate" in the somewhat vague hope that such a change would be beneficial and that through this "short cut" the physician could thus be relieved of a troublesome responsibility. It is obvious then, that patients should first get proper medical and allergic management before climatotherapy is considered. Those patients who have considerable production of mucus are likely to do well in very dry areas, whereas the so-called "dry asthmatic" with or without infection can anticipate generally only further trouble in arid climates. The reverse is true in the moist climates, as we see in Florida.

One must also consider the social, financial, and emotional structure of the patient and weigh these factors against his chances for improvement. We have seen several unfortunate instances of what such enthusiasm for climatic change has done in the way of destroying the security and emotional stability of patients who have attempted such a move, often with no results and sometimes with disastrous effects. In deciding which patients are likely candidates for climatotherapy, one should consider only those that classify as treatment failures and those whose symptoms cannot be ascribed for the most part to irreparable damage, such as emphysema and/or fibrosis. Those patients that fit into this category are evaluated as to the severity of symptoms and the degree of disability. These considerations are weighed against the chances for improvement and the difficulties coincident with the various familial and economic problems brought on by dislocation. Having decided that some change is desirable, the physician must give a great deal of further consideration to the location to which the patient must go. Information such as may be revealed by studies similar to this one will be helpful in this connection.

SUMMARY AND CONCLUSIONS

1. Geographic factors in the area under discussion are the location of this zone in a "storm belt" affecting general weather conditions, the presence of major rivers which influence humidity and flora, and the rough terrain which affects the turbulence of winds and air currents.

2. The climate is generally temperate, but the temperature range is from 0° F to 100° F. The mean daily range is about 20°. There are abundant sunshine, many cloudless days, and generally mild winds. Humidity levels tend to be somewhat above average though not unusual.

3. Air contaminants include industrial irritants and smoke, which have been reduced somewhat by smoke control legislation.

4. The manner of removal of air contaminants depends on natural methods of rain washing, horizontal dispersion by wind, and upward dispersion by air currents. There are undesirable, but fortunately short, periods of air stability that develop in this area.

5. Pollen free resorts are not known in this area.

6. Climatotherapy should be a highly individualized form of treatment which is of unquestionable value in carefully selected patients.

119 Fifth Avenue

COMPANY AIDS FLOOD VICTIMS

Eli Lilly and Company, in accordance with its long-established policy, is replacing all Lilly products in pharmacies and hospitals ravaged by the flood in the Missouri and Mississippi River Valleys. Lilly representatives in a dozen states, from Montana to Missouri, have been directed to make the replacement of flood-damaged Lilly pharmaceuticals and biologicals their first order of business. Eli Lilly and Company has been replacing stocks damaged by uninsurable hazards as far back as the 1906 San Francisco disaster.

Along with the replacement of stocks, the Lilly company maintains a reserve supply of typhoid vaccine and other biological products which is kept ready for fast shipment during disasters. The shipping personnel of the company stands by twenty-four hours a day.

PRACTICE AVAILABLE

A physician specializing in allergy and dermatology in a Midwestern state is contemplating terminating the private practice of medicine. He will dispose of his practice and furniture at a very reasonable figure. Those interested should write to the Assistant Managing Editor, ANNALS OF ALLERGY, 401 La Salle Medical Building, Minneapolis 2, Minnesota, for further information.

ALLERGY FROM THE OTOLARYNGOLOGIST'S VIEWPOINT

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IT has become increasingly apparent to the otolaryngologist that allergy plays a prominent, even a predominant, role in his relationship to and treatment of patients. Briefly discussed here will be observations concerning allergy from the viewpoint of an otolaryngologist.

Consider, first, external otitis. For a number of years, the terms *external otitis* and *fungus of the ear* have been used synonymously. No true fungus disease has existed in 90 per cent of cases of external otitis which have come to the author's attention. Many patients, however, have had a mixed type of bacterial flora.

Response to treatment not meeting expectations, allergy was considered as the possible cause of some of the inflammations of the external ear. Most of the patients who thought they had a fungus infection of the ear complained of itching. A number of them, therefore, were placed on antihistaminic therapy with one 4 mg Chlor-Trimeton Maleate* tablet three times daily. On their repeat visits, it was somewhat startling to note that the itching as well as the skin condition had cleared to a marked degree. Because of this definite improvement, a general allergic work-up seemed to be indicated. It revealed in some instances positive sensitivities, as shown by the following example.

Mrs. F. S., a forty-three-year-old housewife, was first seen on March 1, 1950, with a chief complaint of itching ears and drainage of seventeen years' duration. Numerous otolaryngologists had applied local treatment with only fair results. There was no personal history of allergy; however, her family history was significant in that her father had hay fever. Examination of the ears showed a seborrheic type of skin infection bilaterally, confined to the external canals. Except for lacking luster, the ear drums were within normal limits. The examination otherwise was negative. Culture from the ears showed the presence of Pseudomonas. Upon test, the organism showed sensitivity to streptomycin, extreme resistance to aureomycin, and a tendency to resistance to penicillin. Initially, 1 gm streptomycin solution was applied locally to the ears for three days. The condition grew worse. The patient, on test, showed marked sensitivity to dust, egg, wheat, milk, chocolate, and oranges. The offending foods were eliminated and the patient placed on a dust regimen. She received dust and histamine desensitizing injections and simultaneously 4 mg of Chlor-Trimeton Maleate orally three times a day. The ears improved markedly in four to five weeks; after six months they appeared entirely normal. The ears continue normal and are secreting cerumen for the first time in eighteen years.

As for the other ear problems, patients frequently complain to the otolaryngologist of blocked ears and tinnitus. Complete examination revealing nothing remarkable, a nasal smear is taken. Eosinophils often are found.

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*Chlor-Trimeton Maleate was furnished by M. William Amster, M.D., Schering Corporation, Bloomfield, New Jersey.

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Definite improvement can be achieved by treating such a patient on the basis of an allergy. Consideration of problems of the inner ear reaches into the realm of Ménière's disease. Here, too, good results can be obtained by attacking the affection from an allergist's viewpoint.

It probably can safely be stated that in the majority of allergies, nasal symptoms are at some time the chief complaint. A nasal smear always is taken in my practice whenever nasal symptoms prevail. It is most gratifying to see a patient, treated for a cold for months or even years with penicillin or other antibiotics, whose nasal smear is loaded with eosinophils, respond to allergic management and to realize that the relief has been effected through finding the actual cause.

Colds and coughs constitute another problem for the otolaryngologist, as illustrated below.

Mrs. C. H., a seventy-one-year-old white woman, was referred to me by another physician. Cough of three to four months' duration was the chief complaint, with some question as to the presence of asthma. Treatment with penicillin, then aureomycin, terramycin, and finally chloromycetin had produced no favorable result. The cough became so bad that the patient began spilling urine and had a decidedly disturbing odor about her. When first seen, the cough produced a thick gray, mucoid material. The patient denied any history of hemoptysis or weight loss. Past history and family history were negative for allergy. The entire examination, including x-ray of the chest, was essentially negative except for some increase in peribronchial infiltrate. A nasal smear proved nonspecific. However, a smear of the sputum showed it to be loaded with eosinophils. A complete allergic workup with a culture of the sputum was done. The patient exhibited a 3+ sensitivity to Monilia. The culture showed a heavy growth of yeastlike organisms, resembling Monilia and resistant to antibiotics. Treatment consisted of desensitization to Monilia and the administration of potassium iodide. At the present time, the patient is entirely asymptomatic after having been treated approximately three months.

Other affections, probably as outworn as fungus infection of the ear, are sinus complaints and headache. From the author's experience, he believes the true cause of complaints referable to the sinuses to be not infection but allergy in 50 or even 75 per cent of cases. Handled as allergies, as these cases should be, the responses usually are excellent. Again, the nasal smear is invaluable in diagnosis. Allergy also plays an important role in headache. The importance of a thorough history as well as a physical examination is recognized. When the examination of blood pressure and sinuses is negative, the investigation should be continued elsewhere. If pain is confined to one side of the head, an histamine, migraine, or trigeminal neuralgic type headache should be considered. If an histamine type suggests itself, an allergic work-up is indicated. An example of the latter is cited below.

Mr. G. I., a forty-two year-old white man, was first seen April 20, 1950, a chief complaint of headache. The patient, an automobile parts salesman, for the past twenty years had been annoyed by frequent, sudden, short attacks of right-sided

headache with subsequent blockage of the nose on that side and occasionally lacrimation. The headaches sometimes awakened the patient from a sound sleep; he obtained relief only by getting out of bed. He experienced no aura, nausea, or vomiting with the attacks. Physical examination and blood pressure showed nothing remarkable. A skin test of the patient showed a 3+ sensitivity to baker's yeast. Histamine tests were as follows: 1:100,000—4+; 1:1,000,000—3+; and 1:10,000,000—2+. Baker's yeast was removed from the diet, and histamine desensitization injections were administered for five weeks. The patient became asymptomatic in two weeks. He has had no headaches for nearly a year, during which time he has had no baker's yeast.

In regard to the throat, the author recommends that in cases of nonspecific pharyngitis with a postnasal drip, the secretion be studied under a microscope. Not infrequently eosinophils will be picked up in the nasal smear.

Finally, with regard to endoscopy, the following case is cited.

Mr. E. H., a fifty-two-year-old white man, was a retired butcher, with chief complaints of cough, wheezing, and blockage of the nose. The patient had marked respiratory difficulty. Chest expansion was less than 1/2 inch. Wheezing was marked bilaterally with the exception of the region of the right lower lobe, where breath sounds were absent. The nasal mucous membranes were pale and boggy. Nasal smear showed many eosinophils. X-ray examination of the chest revealed almost complete atelectasis of the right lower lobe. Bronchoscopy was immediately performed. A thick, tenacious, mucopurulent material was washed from the right lower lung field. X-ray examination immediately following the bronchoscopy showed the right lower lung field to have expanded. Within an hour, the chest expansion increased from 1/2 to 2¾ inches. The smear taken from the washings was filled half with polymorphonuclears, half with eosinophils. For this reason, the patient was treated from an intrinsic viewpoint to clear up the bacterial phase. Extrinsically, he was found sensitive to dust and to Alternaria and was treated accordingly with good results. Since the patient did not return for further treatment, nothing is known of his status during the past three or four months.

SUMMARY

A working knowledge of the role played by allergy in the practice of otolaryngology is of major importance to the physician and to the patient. Many patients with external otitis or so-called fungus of the ear, who responded poorly to usual treatments, were shown by allergic tests to exhibit positive sensitivities.

Frequently in cases of blocked ears, tinnitus, nasal symptomatology, cough, colds, sinus complaints, headache, complaints referable to the throat such as nonspecific pharyngitis, and those requiring endoscopy, hypersensitivities can be demonstrated when examination otherwise reveals nothing significant. In such instances, the nasal smear and the microscopic examination of secretions are valuable diagnostic aids.

Vanskike Building

THIAMINE INTOLERANCE

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ALTHOUGH thousands of injections of thiamine hydrochloride are given daily, there are relatively few reports concerning reactions, toxic or allergic, to this substance. Those few reports of intolerance which have been published cannot be completely ascribed to hypersensitivity alone. Since thiamine is a constituent of almost all vitamin preparations taken by a population whose allergic manifestations are estimated to occur in about 10 per cent, it is expected that reports of such reactions would be many. A review of the literature (Table I) indicates the incidence, type of reactions, dose levels at which they occur, and routes of administration. During the last fifteen years only 203 cases have been reported, among which two were fatal. From the data available, the majority of toxic effects from thiamine occur in nonallergic individuals, and it is therefore very difficult to explain such reactions as caused by hypersensitivity alone.

Despite the reports noted above, there are others which include much larger groups of patients and even those with clinical allergies that were treated with thiamine over extended periods of time in whom no untoward effects were produced (Table II).

In face of the latter evidence, it is apparent that there must be some explanation, other than allergy, to account for the reported undesirable actions of thiamine hydrochloride.

The present paper describes two additional cases. These received intensive parenteral thiamine therapy and presented clinical courses resembling some of those indicated in the first table, and which might have been added to the literature as thiamine allergies. Detailed study of these patients stimulated the authors to search for a more adequate explanation for the reactions presented.

Case 1.—Patient O.W.Z., a white male clerk, twenty-five, Italian born, was involved in a motor accident on February 17, 1946.

The laboratory studies of blood and urine showed both to be normal. There was no history of allergy, personal or familial. At the time of study the patient presented (1) a post-concussional syndrome, (2) peripheral nerve injury with a paralysis of the left obicularis oris and nasalis muscles, (3) a traumatic synovitis of the temporomandibular joint, (4) a lumbosacral sprain, (5) a healing fracture of the nasal bones, and (6) myopia.

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TABLE I. THIAMINE INTOLERANCE

Reference	No. Cases	Previous Illness	Previous Dosage				Interval	Precip. Dose			Reaction
			Oral	Subcut or I.M.	I.V.	Total		Oral	I.M.	I.V.	
Steinberg[56]	5	Arthritis	2.4mg/d		6.0mg/wk	232.2mg	1-7 days				Herpes zoster after 7 mos. Spontaneous clearance in 5 wks. Repeated with same results.
		Arthritis	2.4mg/d		6.0mg/wk	38.4mg	1-7 days				Herpes zoster after 5 wks. Spontaneous clearance in 3 wks.
		Arthritis	3.6mg/d			22.0mg	1-7 days				Herpes zoster after 2 mos. Spontaneous clearance in 2 mos.
		Arthritis	2.4mg/d		6.0mg2/wk		4 days			6.0mg	2 min. after last injection—constriction in throat, epigastric fullness.
		Arthritis	2.4mg/d		6.0mg2/wk	99.8mg +	4 days			6.0mg	After last injection—constriction in throat, cramps.
Schiff[46]	1	Arthritis Raynaud's Disease		25mg2/wk		1450mg	30-7 days				2 min. after last injection (58th)—nausea, vomiting, rhinitis, voiding, perspiration, collapse, stopped breathing. Recovered. Five days later scratch test +, wheal, pruritus, nausea, coughing, scratch test 3½ wks. + 4½ wks. +, P.K. test, 2 mos. −.
Mills[32] (a)	1	?		10mg/d		340mg	1 day				After last injection, headache, irritability, insomnia, tachycardia, weakness, trembling, spontaneous clearance in 2 days. Return of symptoms after 4.5 wks. at 5mg/day.
(b)	+?	?		10-50mg		?	daily?		?		Nausea, vomiting. Symptoms similar to hyperthyroidism. One fatal and several others near collapse.
Laws[23]	1	Fractured radius		25mg/d + 25mg/wk		250mg + 225mg	10 days				30 minutes after last injection—urticaria, dyspnea, wheezing, cyanosis. Relief with epinephrine. Intraderm. test +. P.K. test +.
Stiles[58]	2	?	2 yrs. B1 +?	8-10mg2/wk		344-1740mg	4-14 days				3 minutes after injection, weakness, fatigue, recovery. In 4 days—tachycardia, flushing. In 2 wks.—nervousness, tachycardia, flushing, recovery spontaneous. Intraderm. test +. Hyposensitized.
		?	3 yrs	3yrs + 20-50mg		? + 60-150mg	3-4 days				One hour after each injection—warmth, perspiration, tinnitus, agitation. Recovery. Orally mild symptoms. Intraderm test +.

TABLE I. THIAMINE INTOLERANCE—CONTINUED

Reference	No. Cases	Previous Illness	Previous Dosage				Interval	Precip. Dose			Reaction
			Oral	Subcut or I.M.	I.V.	Total		Oral	I.M.	I.V.	
Eisenstadt[8]	2	Peripheral Neuritis	?	25mg2/wk		350mg	60-3 days		25mg		After last injection—local swelling and pruritus. Same after previous injection but milder. Intraderm. +. P.K. test +. Later tolerated orally.
		?		25mg/d + 25mg/wk		600mg + 1100mg	7-10 days		25mg		5 minutes after injection—edema of tongue, eyes, lips. Pruritus, flushing, sneezing. Stopped by epinephrine. Next week only mild reaction. Later, orally without reaction.
Leitner[24]	2	Hypertension Asthma Herpes and Asthenia		? + 25mg/wk		for 4-5 yrs + 100mg	10-9 days		25mg		Dyspnea after injection. One hour after last injection—asthma, fall in blood pressure, thumping in chest, pale. Intraderm. +. Spontaneous recovery. Skin test in 4 wks. Later tolerated oral and parenteral injections without reactions.
		Colitis, Polyneuritis Avitaminosis Neurasthenia		? + 25mg		? + 50mg	? 10-9 days		25mg		After injection, excited, tremors, insomnia, headache, palpitation, vertigo. Spontaneous recovery.
Mitriani[35]	1	Asthma, Rheumatic Fever		50mg/d		300mg	1 day		50mg		After each injection—urticaria. Intraderm. +. P.K. test +. Hyposensitized to tolerate 100mg/d. Intraderm. test in 3 months −.
Reingold & Webb[43]	1	?			100mg	400mg	3-17 days			100mg	After first injection—generalized burning, perspiration. Two more without reaction. Last injection—burning sensation, profuse perspiration, dyspnea, cyanosis. Death. Autopsy.
Stein & Morganstein[55]	1	Alcoholism, Peptic Ulcer		45-90mg		495mg	3-30 days		90mg		15 min. after each injection—pruritus and wheal lasting several hours. 30 sec. after last injection—generalized pruritus, weak, cold, profuse perspiration, dyspnea, irrational, rapid feeble pulse, unconscious, wheezing. Recovery after epinephrine. Intraderm. +.
Englehardt & Baird[9] Baird & Englehardt	1	?		10mg2/wk + 100mg2/wk		120mg + 1800mg	3-20 days		50mg		Previous injection—restless, nausea, vomiting, Last injection—weakness, rapid pulse, substernal constriction, dyspnea, generalized pruritus, urticaria, conjunctivitis, relieved by epinephrine. P.K. test +.

TABLE I. THIAMINE INTOLERANCE—CONTINUED

Reference	No. Cases	Previous Illness	Previous Dosage				Interval	Precip. Dose			Reaction
			Oral	Subcut or I.M.	I.V.	Total		Oral	I.M.	I.V.	
Shapero & Gwinner[50]	1	Nervousness		? + 100mg		? + 3100mg	?		50mg		After last injection—urticaria, dyspnea, wheezing, collapse, recovery after epinephrine. Scratch and P.K. test +. In 15 months skin tests −.
White[63]	3	Arthritis		25mg		?	?		25mg		Anaphylactic shock in one and angioneurotic edema in another few minutes after injection.
Weigand[62]	179	Summary of Complaints from 143 physicians over 11 yr. pd.	?	?	?	?	?	?	?	?	List of 71 symptoms and signs of toxic effects. Most reactions after intravenous injections.
Armanino & Scott[3]	1	Neuritis			?	?	4 mos.			10mg	After 2 injections—wheeze, pruritus. 3 injections 4 mos. later in 2-4 minutes—dyspnea, cyanosis, pallor, perspiration, wheeze, cough, expectoration, bloody sputum, pain in chest and abdomen, hypotension, tachycardia, bloody stools, collapse. Recovery after epinephrine, ACTH, Vit. K., atropine.
Chitwood & Moore[6]	1	?		100mg	?	1 yr	?			100mg	After last injection—muscular contractures, cyanosis, no pulse or blood pressure. Respiratory arrest. Recovery after epinephrine, O_2, then headache, nausea and vomiting.
Total Non-fatal Fatal	203 2										

TABLE II. THIAMINE TOLERANCE

Reference	No. Cases	Dosage				Interval	Comments
		Intra-spinal	Subcut. or I.M.	I.V.	Total		
Williams and Spies[64]	Many?		500 ng/d		15000mg	1 day	No evidence of toxicity
Stern[57]	28	1-100 ng					All patients felt better and rejuvenated
Joliffe[18] Borsook	3000 + 70		10-50 ng	100mg/d	?—7 yrs. 78200mg	1-14 days 1-3 days	No toxic effects observed. Reactions from preservative No signs of toxicity
Kuo and Hwang [22]	2		10 ng		?	?	After last injection—eczema. Skin + reaction due to preservative
Bicknell and Prescott[4]	Thousands		5-150 ng		?—7 yrs.	?	Not a single case of intolerance
Ruskin and Decherd[44]	Over 1000 inject.			300mg		?	No toxic effects noted
Morehead[38]	8			30-40 ng	3000mg	q. 6-8 h. later — q.d.	Complete recovery in six months Chr. bronchitis and severe asthma

He was given seven weekly subcutaneous injections of 50 mg of thiamine hydrochloride. The dose was increased to 100 mg given intramuscularly during the next four weekly injections. At the instance of this last injection, the patient complained of severe nausea lasting for about five minutes after the injection. Two more weekly injections of 100 mg were given intramuscularly with complaints of nausea, the only difference being that with each subsequent injection the nausea persisted for a greater length of time. These last two injections were from a different commercial preparation. The following week another injection intramuscularly of 100 mg was given, and severe nausea was experienced immediately after injection. Epinephrine (1:1000) 0.2 cc was injected five minutes after the thiamine with prompt relief. The following week the patient refused to take thiamine for fear of a reaction. However, the patient was convinced of the necessity of having the injections and finally acceded. Sterile saline solution injected subcutaneously was not followed by nausea. The patient was skin tested by the scratch method with a 1:10 (100 mg/cc) extract of thiamine hydrochloride, which gave a positive reaction. He was placed on a regime of 100 mg daily of thiamine hydrochloride orally. He complained that he experienced nausea at regular intervals during the day, especially after eating, as well as profuse perspiration during sleep. There was no vertigo. He had himself noted that he was not as irritable as he had been previously.

A blood specimen taken at the time of skin testing revealed the following: P.K. +, control +. (.02 cc of 10 mg/cc = .2 mg). A scratch test three months later with a fresh extract was unchanged. The dosage of thiamine hydrochloride was reduced to 5 mg orally daily. Oral doses were discontinued in six weeks. At this level, no nausea was experienced. Since this time he has taken B complex twice for four to six weeks without a reaction.

Case 2.—Patient E. Z. was a white female twenty-four years of age, married to above patient O. W. Z., born in New York, occupied as a stenographer and housewife, and involved in the same accident.

The history was noncontributory except those incidents relative to the present illness, wherein she suffered from a postconcussional syndrome, multiple lacerations of the lower extremities, a peripheral nerve injury of the left leg with consequent foot drop, and traumatic synovitis of the left ankle. There was no personal or familial history of allergy. Laboratory examinations of blood and urine showed these to be normal.

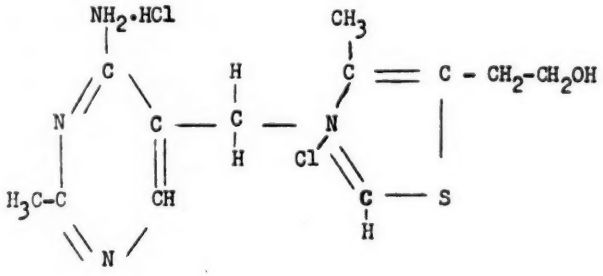
In addition to her physiotherapy, for seven weeks she received 50 mg of thiamine hydrochloride subcutaneously. The subsequent four weekly injections of 100 mg were given intramuscularly. After the last injection she complained of severe nausea and also that she felt nervous and had vertigo. The next week she was given another intravenous injection of 100 mg of a different commercial preparation, without a reaction. The following two weeks she was given 1 cc of caffeine sodium benzoate intramuscularly, even though told she was getting the same medication. There was no complaint of nausea, although she said the site of injection hurt. A "sterile hypo" was then given. A scratch test of thiamine hydrocloride extract, 1:10 (10 mg/cc) was positive. A blood specimen at this time showed P.K. +, control +. The patient was placed on a regimen of 5 mg of thiamine hydrochloride orally. This was tolerated without nausea for a period of two months. Medication has since been discontinued due to the improvement of her peripheral neuritis. A scratch test three months later with a fresh extract was unchanged. She since has taken B complex six times as a vitamin supplement for periods ranging from three to ten weeks, without a reaction.

It is curious to note that both patients began to show toxic effects after having received a total of 650 mg of thiamine parenterally. Psychogenic

factors were eliminated by using other medications and placebos unknown to the patient as well as by the use of two different commercial preparations.

PHYSIOLOGY AND CHEMISTRY

Since thiamine was isolated from natural sources,[67] synthesized,[64] and both shown to be identical,[7,28] it was accorded quick acceptance and widespread use in therapy.



Thiamine Hydrochloride - $C_{12}H_{17}N_4OSCl \cdot HCl$ - Mol. wt. 337.26

The compound, colorless monoclinic crystals having a melting point of 248°–250° C, is soluble in water and alcohols, relatively stable to dry heat but destroyed by autoclaving and by sulphites.

The pyrophosphate ester of this vitamin is cocarboxylase which participates in all oxidative decarboxylations leading to the formation of CO_2. Thiamine and other members of the B complex group are essential constituents of co-enzyme systems involved in normal intracellular respiration[25] of the nervous system, in synthesis of acetylcholine, and in the processes of growth, fertility and lactation. It is necessary in the metabolism of carbohydrates principally by furnishing cocarboxylase so that pyruvic acid can be further broken down to acetaldehyde, then to CO_2. Thus any stress factors that produce anoxia and shock require the presence of thiamine as well as phosphorus, calcium, potassium, and manganese to insure the integrity of the enzyme sytems.[68] Through these enzyme systems thiamine is also concerned with protein and phospholipid synthesis.

In deficiency states the carbohydrate mechanism is impaired, causing an accumulation of pyruvic acid in the tissues. Clinically, deficiency is manifested by (1) cardiac beriberi with enlarged heart, diminished vital capacity, abnormal rhythm, reversal of T waves, and prolonged Q-T interval, (2) "wet" beriberi with generalized anasarca, (3) "dry" beriberi with perpheral neuritis, anesthesia and hyperesthesia, atrophy of muscles, degeneration of nerve fibers, brain lesions, convulsions, increase in amplitude of brain waves, and (4) gastrointestinal disturbances with achlorhydria,

dysphagia and gastric atony. In view of these manifold symptoms and signs, in addition to the acknowledged incidence of malnutrition with "subclinical" avitaminosis in our population, it is no wonder that thiamine is used so widely.

It is fairly well established that thiamine is stored in great quantities, that it can be demonstrated in the myelin sheath of nerves, and that this is where acetylcholine synthesis takes place.[39] It is also found that the acetylcholine content of nerve tissue decreases in the thiamine-deficient animal.[27]

On injection of thiamine, there is a massive synthesis of cocarboxylase in the liver.[66] Whenever it is necessary for the body to replace the depletion in circulating free thiamine or its monophosphate, there is a hydrolysis of the cocarboxylase stores. Accordingly, most of the thiamine in the body is present as cocarboxylase, and only about 0.5 micrograms per 100 cc of blood are found in the free state. If more than optimum needs are given, the excess is rapidly destroyed or excreted.[12] The daily requirement for an adult is 1 to 2 mg per day.

When large amounts of thiamine are injected intramuscularly, the bulk is excreted, mainly in the urine, in the next three hours.[29] However, excretion is lowered in diseased subjects, who show an output of only 4-10 per cent in twenty-four hours. Even in normal subjects excretion varies with the mode of administration and dose; i.e., with 50 mg given subcutaneously, only 10-20 per cent was excreted in twenty-four hours.[48]

Thus a condition can exist where there is an accumulation of thiamine excesses which may produce toxic effects, especially when significantly large doses are given daily or at frequent intervals in individuals who have impaired excretion.

PHARMACOLOGY

Thiamine has definite pharmacologic as well as metabolic effects when given in large doses, especially in conditions where there is no evidence of deficiency. It can produce a diuresis through a central effect[14] as well as increasing the tone of the ureters, large intestine, and rectum,[47] even in small doses; it increases the peristalsis of the small intestine and causes spasm in skeletal muscles, weakness, and tetany.[28] Cardiovascular effects are well annotated; small doses raise the blood pressure,[28] while large intravenous doses cause a marked bradycardia, vasodilation, and hypotension through a central effect and not on the blood vessels themselves.[10,20,36] It is felt by most that respiratory disturbances leading to complete inhibition are associated concomitantly with the cardiovascular effects.[37,51,57,60] It is interesting that thiamine in excessively large doses (150 mg/Kg) produces effects of neuromuscular block typical of curare. Conversely, 0.15 mg/Kg of D-tubocurarine can mimic all the toxicity effects of thiamine but produces a longer lasting neuromuscular block.[52] This might indicate that when thiamine is given rapidly intravenously in large doses the toxic

effect is predominantly due to its "curare-like" action upon the autonomic ganglia, especially the parasympathetic.[53]

During the process of nerve stimulation the ester, and even thiamine, along with acetylcholine are formed.[26] However, the naturally occurring acetyl ester of thiamine itself can produce effects on tissue like acetylcholine.[21,45] Thiamine intensifies and augments the action of acetylcholine as seen in isolated heart and gut experiments[1,16] and in the stimulation of nerve trunks.[33] It has been shown further that thiamine is essential to the transmission of nerve impulses, since it enhances the activity of acetylcholine at nerve endings by inhibiting the formation of the enzyme cholinesterase.[5,34,40,41,61] It is known that blood levels of cholinesterase are increased in the presence of thiamine deficiency and that cholinesterase formation is inhibited by thiamine.[30,59] This is particularly true when an amount of thiamine is given which exceeds the normal amount in the tissues so that the degree of inhibition of cholinesterase can be readily measured in the serum.[11]

A further detailed review of the pharmacology of acetylcholine reveals that when excessive amounts of this substance are allowed to exist unantagonized by cholinesterase, symptoms and signs of hypersensitivity states and allergic disease are reproduced, even to the details of the pathological changes.[17] Recent studies[31,49] show that allergic states, such as asthma, are coincident with high blood acetylcholine levels. Large doses of thiamine (100 mg/Kg intravenously) will cause a slight bronchoconstriction, some of which can be blocked by Benadryl.[54] This experiment implies that, in some susceptible patients, toxic effects may be due also to the liberation of histamine.[42] Thiamine cocarboxylase is high in concentration in the same organs (liver and kidney) as are the histidine decarboxylase, which might infer a relationship in the formation of excessive amounts of histamine as well as acetylcholine in the tissues.[15] However, acetylcholine itself does induce the release of histamine.[2]

In an attempt to elucidate this problem, further experiments were designed to study and compare the effects of thiamine, acetylcholine, and histamine in the same animal as well as to make an attempt to evaluate various forms of therapy to combat the toxic effects produced. Since the respiratory and cardiovascular changes have been shown to be concomitant and consistent,[43] it was decided that blood pressure changes alone would be used as an index of the central effects of thiamine.

MATERIALS AND METHOD

Adult dogs ranging in weight from 5 to 10 Kg were anesthetized intraperitoneally with either Dial or Nembutal. Blood pressure was measured with a mercury manometer attached to a canula in the carotid artery. Fresh buffered thiamine hydrochloride (B. W. & Co.) 100 mg/cc in various doses was injected into the femoral vein. Other freshly made solutions injected

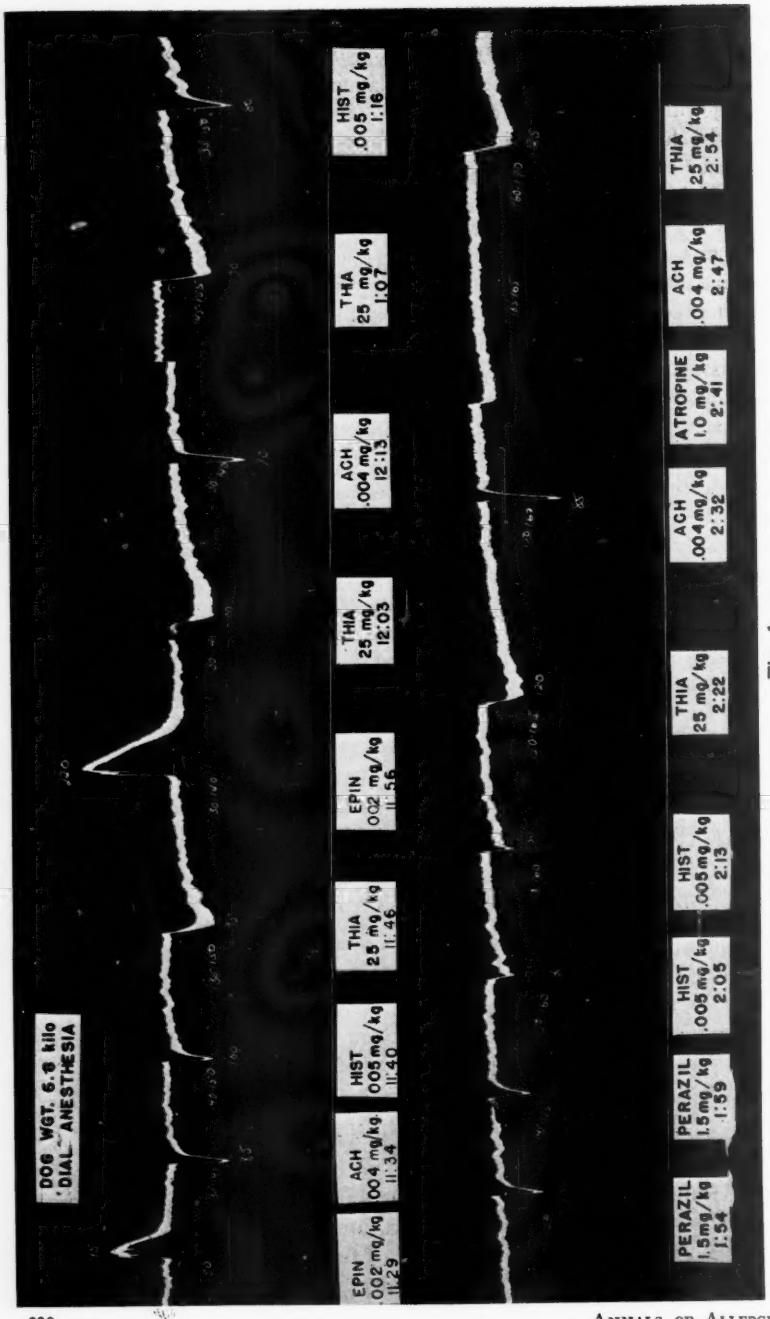

DOG WGT. 6.8 kilo
DIAL ANESTHESIA
EPIN .002 mg/kg 11:29
ACH .004 mg/kg 11:34
HIST .005 mg/kg 11:40
THIA 25 mg/kg 11:46
EPIN .002 mg/kg 11:56
THIA 25 mg/kg 12:03
ACH .004 mg/kg 12:13
THIA 25 mg/kg 1:07
HIST .005 mg/kg 1:16
PERAZIL 1.5mg/kg 1:54
PERAZIL 1.5mg/kg 1:59
HIST .005 mg/kg 2:05
HIST .005 mg/kg 2:13
THIA 25 mg/kg 2:22
ACH .004 mg/kg 2:32
ATROPINE 1.0 mg/kg 2:41
ACH .004 mg/kg 2:47
THIA 25 mg/kg 2:54

Fig. 1

into the femoral vein were acetylcholine 1/10,000 (0.004 mg/Kg), histamine 1/10,000 (0.002–0.005 aver. 0.004 mg/Kg), Pyribenzamine (5 mg/Kg), Benadryl (5 mg/Kg), Perazil (3 mg/Kg) and epinephrine U.S.P. 1/20,000 (0.002 mg/Kg). Thiamine was given in 1, 2, 5, and 25 mg/Kg doses. Even though definite responses are obtained with the 1 and 2 mg/Kg doses (comparable to the dose in humans), the majority of the records obtained are with the 5 mg/Kg dose, since this level better illustrates the effect of thiamine while approximating the dosage used therapeutically.

RESULTS

On injecting thiamine 25 mg/Kg, acetylcholine, and histamine, there is noted a uniform and equivalent fall in blood pressure; the effects of these are all equally reversed by epinephrine. It is interesting to note that epinephrine response after thiamine is slightly exaggerated over the control, suggesting a sensitization of epinephrine effect by thiamine. If the blood pressure fall produced by acetylcholine is blocked by atropine, thiamine continues to cause an independent hypotension. The same separate effectiveness of thiamine is seen although the histamine effect is blocked by Perazil (Fig. 1). When 5 mg/ Kg thiamine is injected at the maximum blood pressure fall produced by acetylcholine, there is a further drop in blood pressure. The same result is obtained when thiamine is added after histamine (Fig. 2). This summation effect is completely reversed by epinephrine.

The injection of 5 mg/Kg of thiamine causes a fall in blood pressure that is equivalent to 0.005 mg/Kg of histamine. Perazil in one 1.5 mg/Kg dose effectively blocked the histamine response but did not inhibit the response to thiamine. If the antihistamine Perazil is added at the point of maximum blood pressure fall produced by thiamine, there is an additional hypotension produced (Fig. 3). Changing to the ethylenediamine antihistamines Pyribenzamine (Fig. 4) and Benadryl (Fig. 5) produced changes no different from those seen with Perazil.

After obtaining control responses to epinephrine, acetylcholine, histamine, and thiamine (5 mg/Kg) epinephrine was given at the peak of blood pressure fall produced by thiamine. Again it is noted that there is a suggestion that thiamine sensitizes the effect of epinephrine by the flattening of the epinephrine curve, indicating the prolongation of effect and similar to that seen at the higher dose of thiamine in Figure 1. When acetylcholine or histamine are added at the height of effect from thiamine, there is an added hypotensive response (Fig. 6). Even though Perazil will inhibit the histamine effect it will not antagonize the hypotension from thiamine, which still reacts equal to the control (Fig. 3).

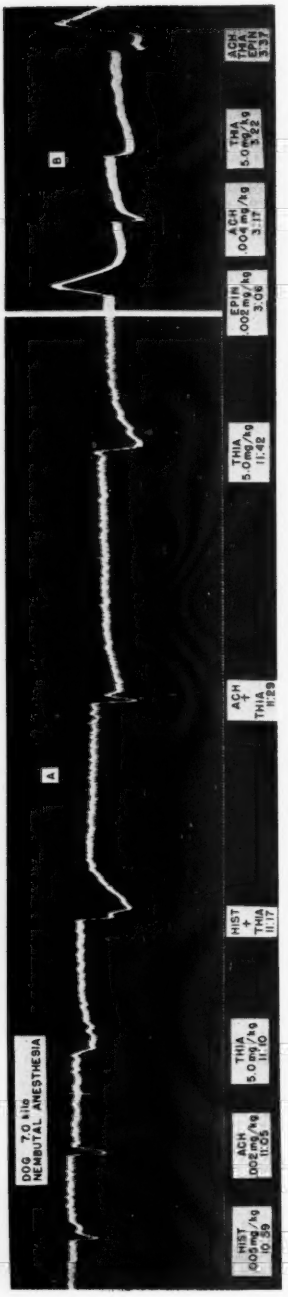

DOG 7.0 kilo
NEMBUTAL ANESTHESIA
HIST .005mg/kg 10.59
ACH .002mg/kg 11.05
THIA 5.0mg/kg 11.10
HIST + THIA 11.17
ACH + THIA 11.29
THIA 5.0mg/kg 11.42
EPIN .002mg/kg 3.08
ACH .004mg/kg 3.17
THIA 5.0mg/kg 3.22
ACH + EPIN 3.37
A
B

Fig. 2

DOG WGT. 10 kilo
DIAL ANESTHESIA
THIAMINE 6.0 mg/kg 1:25
THIAMINE 5.0 mg/kg 1:38
HISTAMINE 0.005 mg/kg 1:53
PERAZIL 1.5 mg/kg 2:07
HISTAMINE 0.005mg/kg 2:16
THIAMINE 5.0 mg/kg 2:26
PERAZIL + THIAMINE 2:35

Fig. 3

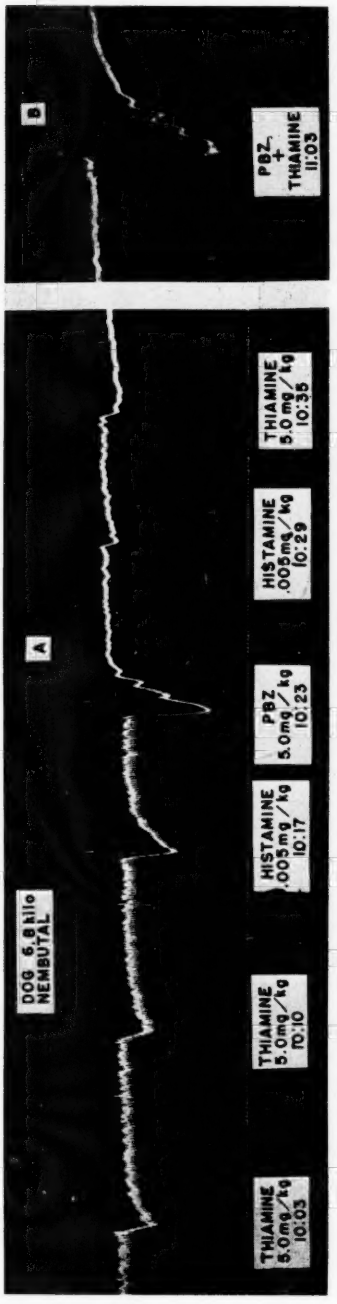

A
DOG 6.8 kilo NEMBUTAL
THIAMINE 5.0mg/kg 10:03
THIAMINE 5.0mg/kg 10:10
HISTAMINE .005mg/kg 10:17
PBZ 5.0mg/kg 10:23
HISTAMINE .005mg/kg 10:29
THIAMINE 5.0 mg/kg 10:35
B
PBZ + THIAMINE 11:03

Fig. 4

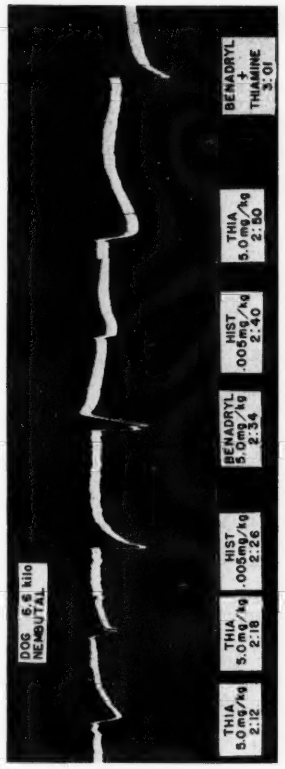

DOG 6.6 kilo NEMBUTAL
THIA 5.0mg/kg 2:12
THIA 5.0mg/kg 2:18
HIST .005mg/kg 2:26
BENADRYL 5.0mg/kg 2:34
HIST .005mg/kg 2:40
THIA 5.0mg/kg 2:50
BENADRYL + THIAMINE 3:01

Fig. 5

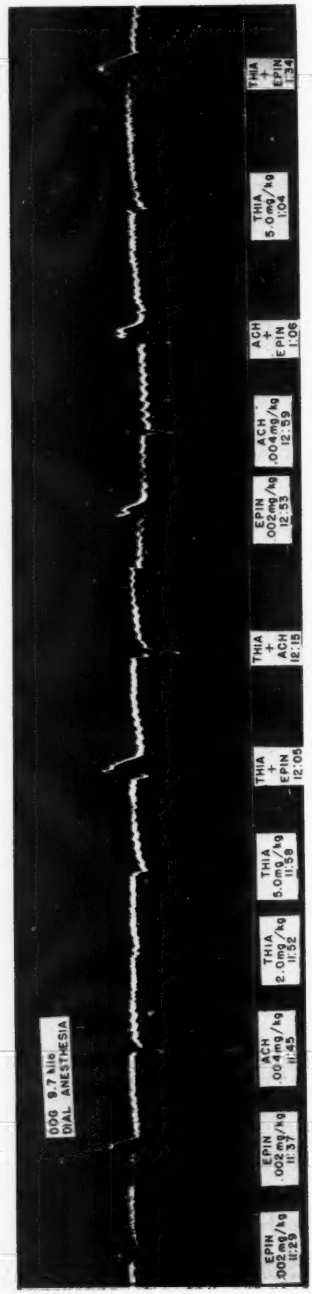

006 9.7 kilo
DIAL ANESTHESIA
EPIN .002mg/kg 11:29
EPIN .002mg/kg 11:37
ACH .004mg/kg 11:45
THIA 2.0mg/kg 11:52
THIA 5.0mg/kg 11:58
THIA + EPIN 12:05
THIA + ACH 12:15
EPIN .002mg/kg 12:33
ACH .004mg/kg 12:59
ACH + EPIN 1:06
THIA 5.0mg/kg 1:04
THIA + EPIN 1:34

Fig. 6

DISCUSSION

Even though there are a number of reports in the literature ascribing intolerance to thiamine upon an allergic basis, the weight of pharmacological and even clinical evidence would indicate considerable doubt that such is the basis for the effects seen. The earliest publications explained the reactions as due to simple overdosage[32b] and irritation of peripheral nerve plates[56] rather than due to hypersensitivity, occurring in only a small percentage of individuals. Such explanation was given by investigators with wide and extended experience for many years: e.g., Jollife,[18] who states, "Doctors Borsook, McLester, Sebrell, Spies and Sydenstricker have informed me that their experiences have been similar." None of these investigators has reported intolerances to thiamine, but remarks were made that some patients might react to the preservatives used in commercial preparations. This latter observation might include many of those cases compiled by Weigand.

Unfortunately, due to the lack of complete details in previous reports, it is impossible to correlate the onset of toxic symptoms, the interval between doses, or the total amount of thiamine necessary to produce such effects.

There is no physiological or biochemical evidence to show that coupling takes place with thiamine to form an azoprotein and thus act as an antigen to cause allergic reactions. As a matter of fact, attempts to sensitize rabbits to thiamine by giving 100 mg doses intravenously showed there was no difference between these and untreated animals[13] and no evidence of anaphylaxis. Curiously it was found that tolerance to thiamine was raised more than two times, in those so previously injected. This latter observation may explain the result obtained in humans and which were ascribed to hyposensitization.

It is useless to perform any type of skin tests since thiamine is a primary urticariogenic agent[19] although in great dilutions just as with acetylcholine and histamine.

Since acetylcholine is intimately associated with both thiamine and the pathogenesis of hypersensitivity states,[17] it is readily understood why the toxic effects of thiamine overdosage could be construed to be due to an allergic reaction. Experimental evidence favors the premise that thiamine overdosage produces a simple chemical toxicity principally through the formation of excessive amounts of acetylcholine and possibly some histamine. Cumulative effects from thiamine overdosage can easily occur by producing undue tissue concentrations of acetylcholine, especially in diseased patients who have an impaired excretion of thiamine and a low physiological tolerance to acetylcholine, thereby manifesting toxic reactions.

Experience indicates that antihistamines do not inhibit the hypotensive effect of thiamine, which infers that this reaction is mediated through acetylcholine almost entirely. Once thiamine has produced toxicity it can

be antagonized effectively by epinephrine and not by most antihistamines, which only aggravate the undesirable responses.

CONCLUSIONS

1. It is difficult to believe that thiamine, an essential vitamin vitally necessary for the integrity of enzyme systems, could act as an allergen to produce allergic reactions.

2. Thiamine is intimately associated with acetylcholine, which can accumulate in excessive quantities in the tissues and cause symptoms of toxicity.

3. Cases and animal experiments indicate that pharmacologic effects of thiamine are identified with acetylcholine and histamine, and can be reversed by epinephrine, which is sensitized by thiamine and not by antihistamines, that actually exaggerate toxic manifestations.

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The United States Air Force has announced a program whereby commissions will be offered to young men and women practicing in all fields of medicine and in all allied specialized vocations.

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Each classification has a different set of requirements for each grade from second lieutenant through the higher grades. The First Air Force has set up clerical facilities for promptly answering all queries concerning these commissions. Inquiries should be directed to the Air Surgeon, Headquarters, First Air Force, Mitchell Air Force Base, New York.

SELF-INFLICTED, FOOD-INDUCED ALLERGIC ILLNESS

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THIS paper reviews some of my clinical experiences of the past ten years with more than 600 patients who had clinically significant food allergies. Many of these patients suffered at one time or another from self-inflicted, food-induced allergic illness.

These patients seek medical attention because they want to find out why they are sick. They spend time and money, and subject themselves to the discomforts of allergic investigation. After searching study by the allergist, the offending foods are tentatively identified, and carefully supervised clinical trials confirm the fact that ingestion of an allergenic food is the actual cause of the patient's allergic illness. When the patient excludes the offending food (or foods) from his diet, he often volunteers that when he abstains from these, he enjoys better health than he has experienced for many years. Yet, in spite of all this, the allergic patient at various times seems to go out of his way to eat the very foods which surely make him sick.[20,23,27]

Why should such a thing happen? What can the allergist as a physician do to prevent the occurrence of such needless, self-inflicted, food-induced allergic illness? These questions have no simple or glib answers. But I want to tell you what I have learned about such problems in the past ten years of my practice. I want to tell you about some of the psychological mechanisms responsible for unconscious or conscious deviations of the patient from the therapeutic regimen recommended by his allergist, because such information is a prerequisite to the development of a therapeutic program intended to prevent a patient from self-injury in the form of self-inflicted, food-induced allergic illness.

Eating is always an emotional experience and for most of us a pleasurable experience. In the course of our lives, we have all developed our personal version of what constitutes good eating. We develop self-satisfying, comfortable, systematized patterns of eating which not only govern our choice of foods but also the manner in which they should be prepared and served, and even the order in which foods should be served. Most of us would be quite unhappy if, on sitting down to dinner, we were served the meal in reverse order, starting with a rich, gooey dessert, and ending with a tangy appetizer.[2,5,21]

When an allergist interdicts the use of specific foods, he interferes with a patient's usual eating habits, with his way of life, and with his ordinary methods of expressing his feelings and symbolically satisfying deep emotional needs through the choice of special foods. The allergist in his capac-

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ity as an authoritarian figure or parental surrogate advises and even orders his allergic patient to eliminate a specific food from his diet because this will prevent food-induced allergic illness and the patient will benefit directly by an improvement in health. This medical approach really constitutes an appeal to the patient's intellectual capacity to understand that if he deprives himself of food which he enjoys eating, from which he derives important emotional gains (secondary or primary), the patient will have freedom from a specific type of allergic illness.

Right then and there, the allergist has set up an ambivalent situation with regard to the eliminated food. The patient likes the interdicted food, he enjoys and relishes eating it, he would like to continue eating it because it has always had some positive values in terms of emotional comforts symbolically derived from eating these foods. But now the doctor says that the foods must be regarded as a noxious agent. A patient finds it very difficult to understand how the chocolate nut sundae which gives him such pleasure is really doing all the dreadful things to his system, thus causing all the troubles which he originally complained about when he consulted his allergist. Emotionally, this delicacy gives comfort if eaten—but at the same time it causes physical and emotional distress as a direct and indirect consequence of the allergic reaction which follows ingestion of an allergenic food.[17,24,25]

Now, what does deprivation of an offending food do to a patient's long-standing habit patterns of eating? What happens to his special emotional need for eating forbidden foods—which are often a patient's favorite foods?

At first, most allergic patients who are placed on a therapeutic diet are like the new broom that sweeps clean. The patient often seems to be able to make profound and personally uncomfortable changes in his diet without too much anxiety—and without too much hostility and resentment toward his allergist.

Offhand, this may seem surprising, because most normal people have developed such systematized, stereotyped, self-satisfying eating habits that it is the very repetitiveness and familiarity of the average way of eating which gives an important type of emotional comfort and security to all of us. I have found that even with a free choice of diet many individuals often select no more than twenty different items of food in any one month's time. In fact, dietary habits are often so structured that any unannounced change in menu is often met with discontent—and, if the change is persistent, it can arouse uneasiness and anxiety.[13,16,18]

Nevertheless, in spite of all this, an emotionally well-adjusted allergic patient makes therapeutically recommended changes in diet rather easily at first. He came to the allergist to be helped—and if this is the way to achieve the goal, it must be done. And for a time, the patient may even enjoy the feeling that he has the strength of character to deprive himself voluntarily of emotionally desired foods. For a time, he may enjoy being a seven-day wonder in his family, social and business groups—he may enjoy

the attention and solicitude he receives from others as a result of his self-denial of favorite foods. Additionally, the patient may return to his allergist for the next check-up and be delighted with the approval he receives from his physician. When the patient reports that he is completely free from formerly troublesome symptoms as a result of abstinence from offending food, the doctor is pleased. Then, being a busy man, the allergist tells his patient: "You have demonstrated to my satisfaction that we have gotten to the root of your allergic trouble. Continue with the same diet and come back to see me in six months—earlier, if you don't feel well." At first the patient may be elated, because extension of time between scheduled visits means excellent progress. But later, he feels rejected by his physician.

Whenever a person tries to change a basic pattern of living, he must have continuing encouragement and recurrent therapeutic suggestions which re-enforce the newly conditioned patterns of living which he is trying to establish to supersede older and more fixed modes of behavior. If a patient feels rejected by his doctor, he has less incentive to be governed by therapeutic suggestions made by his doctor. In fact, under such circumstances the allergic individual is much more susceptible to the urgings of his own emotional needs versus his intellectual understanding of his therapeutic needs. And simultaneously he also becomes more amenable to suggestions of members of his family, friends, business associates, or even strangers who urge him to eat forbidden foods which in their opinion could not possibly cause real illness.[3,28]

If the patient reverts to his original pattern of eating, he again may develop his original allergic illness—and, of course, he can then go with honor to consult his allergist, who again gives the patient much-desired professional attention and direction.

Of course, all this means that in practice the allergist should supervise the patient allergic to foods by seeing him often enough so that he can tell his patient again and again the basic therapeutic instructions, and give the patient emotional support through approval of his actions in abstaining from offending food.

Before considering the patient's emotional needs to eat specific foods, even though he is allergic to these, I would like to call your attention to a convenient table which lists the common emotional use of foods in terms of a patient's likes and dislikes (Table I). For the moment, we do not have to concern ourselves with a patient's food dislikes—except to mention that a patient avoids eating these foods. If he is forced to eat such foods, he usually develops untoward psychosomatic reactions which may need to be differentiated from true allergic reactions. If the allergist asks the patient to eat some of the foods which he dislikes, the doctor will first have to spend considerable time in deconditioning the patient's dislike-reaction, thus making it possible through reconstructive psychotherapy for a patient to learn to enjoy eating a formerly disliked food.[16]

TABLE I.

FOOD LIKES	FOOD DISLIKES
Security foods	Cultural taboo foods
Reward foods	Religious taboo foods
Fetish foods	Familial taboo foods
Party foods	Individual taboo foods
Show-off foods	Unfamiliar foods
Grown-up foods	Unpleasurable-association foods
Pleasurable-association foods	Familiar foods prepared in unfamiliar ways
Familiar foods prepared in familiar ways	Hard-to-prepare foods
Easy-to-prepare foods	Foods with built-in anxiety
Advertised foods	Punishment foods
Foods with agreeable sensory properties:	Foods from filthy sources
Unspoiled foods	Foods with disagreeable sensory properties:
Proper color foods	Spoiled foods
Proper odor foods	Off-color foods
Proper taste foods	Off-odor foods
Proper texture foods	Off-taste foods
Proper temperature foods	Off-texture foods
	Off-temperature foods

A useful classification of foods according to emotionally determined reactions to symbolic or sensory values of specific foods. Attitudes of an individual toward food tend constantly to undergo modifications according ot evolving life experiences and needs, as these can be satisfied or expressed through the use or avoidance of specific foods.

A given food may belong to more than one category in this formulation at any one time. For example, for a given individual, chocolate ice cream may be a security food and a reward food, and if he eats it repetitively in large amounts for exhibitionistic purposes, it becomes for him a show-off food. An individual who uses chocolate ice cream in these ways may at a later time in life develop an aversion to it if he believes that on one or more occasions the overeating of this material made him very sick. Because of this unpleasurable association, he will then avoid eating this food.

Our principal concern with foods used emotionally is with the categories listed under food likes in Table I. Patients learn to enjoy the taste, texture, appearance and odor of certain foods. It gives them gustatory pleasure to eat these foods. One of the chief reasons why an allergic patient eats forbidden foods is that he has a longing to eat and taste what used to be his favorite food, regardless of allergic consequences. Now it really wouldn't be too bad if once in a while an allergic patient did this—except that once he has tasted his favorite food, his old eating habits are so re-enforced that he again becomes addicted to the use of this food. He continues to enjoy the gustatory properties and is willing to pay the price of suffering allergic ill-health for this privilege.[10,29]

What I have done to prevent this pattern of reaction is to tell the patient that in a fixed period of time he will be allowed to eat a test feeding of the allergenic food which he enjoys so much, and that in this way we will be enabled to see if he has developed any significant tolerance to this. And I warn him that if he eats it before this time, he may interfere with the "hyposensitization by abstinence" process. Few patients "jump the gun" by eating the allergenic food before the time designated for testing. Most feel that the allergist under these circumstances is not a hostile, arbitrary physician—but that he is their friend and that he is trying to restore to their diet the allergenic food in amounts and in frequency of eating which will give them pleasure and still not harm them by causing clinically evident allergic reactions.

The next most common cause of self-inflicted, food-induced allergic disease is the patient's eating of such foods as an attempt to deny his allergic weakness. He may be ashamed to admit to others (and be unwilling to admit to himself) that his body can no longer tolerate foods which

it could once handle without causing subjective allergenic discomfort. For this reason alone he may try to deny his idiosyncratic allergic tendencies by overdetermined drives to repeatedly ingest offending foods, and to deny the clinically obvious allergic illness resulting from ingestion of allergenic foods.[2,3,18,28] This denial of bodily inferiority is analogous to that occurring in other types of physical disability.

For example, we know that a man who limps as a result of a persistent deformity of one of his lower extremities may develop both characterological alterations and aberrant behavioral patterns as part of his adaptive reactions to his deformity, in a world made up largely of nondeformed people. In similar manner, a person with the physiological inferiority of food allergy tends to develop characterological and aberrant behavioral patterns as his method of emotional compensation to his allergic illness in a world of people who seem to be able to eat everything they desire without suffering any penalties of idiosyncratic ill-health.[3,18]

In the absence of unusual stresses, an emotionally well-adjusted person can often make a good, realistic adjustment to food restriction without encountering too much personal difficulty. He may rather quickly lose his taste and desire for even foods that were formerly his favorite foods and learn to eat with gustatory enjoyment food which formerly he did not like. He may actually gain ego-strength and comfort from knowing the cause of his troublesome and formerly mysterious ailment and from having the power to control it voluntarily through abstinence from the offending food.

But the lives of most people are not constantly serene. We are subjected to all sorts of stresses and threats to our security. Even a well-adjusted person has from time to time periods of exceptional stress, sorrow, anger, anxiety, pain, depression, elation or guilt; and it is during such times that he is most likely to deviate from any logical program of dietary restriction, even when such deviations lead to allergic illness. The reason for this is that in many people part of the homeostatic response to threatening or stressful situations results in their use of special foods for the symbolic benefits derived from ingestion of these foods.

All of us have our private security foods—usually milk and milk products. Many people who are under severe emotional stress unconsciously increase their intake of milk. Individuals who are allergic to milk often have such a great need for milk when their security is threatened that they will drink it even though it makes them sick.[8,14,15,16]

For example, a patient of mine who did not budget his income properly had a strong need to drink milk—which was for him an allergenic food—whenever he felt his security was threatened. Milk caused him gastric distress within an hour of ingestion and nausea and vomiting several hours later. During a stressful period he drank milk steadily, becoming sicker all the time. He was hospitalized by another physician because it seemed likely that he had an active peptic ulcer—which he did not have. He recovered promptly when milk was eliminated from his diet. After a num-

ber of interviews, we were able to have him externalize some of his feelings by saying that he felt that March 15, income tax time, was a threat to his security, and that unconsciously he craved milk, all the time being afraid that he might have to sell some of his securities, perhaps at a loss, to pay his tax bill. Now, for the past two years I have seen this man several times before January 15, and through talking about his special problems have been able to have him solve his tax problems without needing to resort to milk, his allergenic "security food."

Another category of foods which is hard to abstain from are the "reward" foods. Food has been used as a reward for accomplishment in the training of infants and children, and in this way the idea of the "reward" food permeates many unconscious patterns of self-gratification through the symbolic use of such foods—especially at those times when the individual feels he has received inadequate recognition in reality for his achievements. The reward foods of our culture include chocolate, hot dogs, ice cream, cake, et cetera.

Many people who feel that their work efforts have not been adequately recognized in conventional ways by praise or promotion or increase in salary, or that others have not commiserated them sufficiently for their failures, often unconscicusly eat large amounts of the reward foods and thus assuage their adult feelings of being unappreciated, unsuccessful, or even rejected. Sometimes, it is only when the patient is under unusual emotional stress that he will be unable to resist eating known allergenic reward foods, which during less tempestuous periods he will scrupulously avoid. A person allergic to chocolate may feel such a strong need to reward himself that he seems to have an insatiable desire for chocolate, which he not only eats but actually "binges," often until he has a sufficiently severe allergic illness to require bed rest. Under these circumstances he is rewarded by getting the sympathy and care ordinarily extended to a sick member of a family. As an indirect consequence of the display of affection showed by the family, the individual suddenly loses his need to eat more chocolate—at least, temporarily.

Some patients cannot abstain for long from their "fetish" foods, even though the very eating of these causes severe allergic reactions. "I must eat red meat to keep up my strength," or "I don't feel good unless I have potatoes at least once a day." Sometimes health and advertising writers sell people the idea they must have certain foods to live long, to be healthy and wealthy. This promise is difficult to match, when all the allergist has to offer is freedom from allergic illness through abstinence from these foods.

I will not discuss the emotional uses of the pleasurable association foods, the grown-up foods, et cetera, but instead wish to tell you about certain types of social pressure which cause patients to eat known allergenic foods. An allergic patient may have no difficulty in abstaining from offending foods in his home setting but may not be able to refrain from eating such foods in the social setting of a visit to the home of friends.

Some people feel that they must always conform outwardly to an acceptable pattern of social conduct. They will often eat a known offending food to please a hostess, fearing social disapproval more than allergic illness. Some of these people hate to let others know of their food allergies since they don't want anyone to consider them different from "normal," or inferior in health. Some persons in this group are highly suggestible and cannot reject a positive suggestion that they eat this or that food; they may have a high degree of oral insecurity and much latent hostility which comes out of their unconscious infantile fear of being deprived of some oral pleasure. Such persons cannot easily refuse an invitation to eat a known allergenic food, especially when someone else is providing it or paying for it. Sometimes a patient will be rather easily persuaded to eat an allergenic food if he is hostile toward his hostess, or afraid of her. The hostess says, "This is delicious, you must try it, I made it myself," or, "A little bit won't hurt you," and the individual lets himself be persuaded to eat the allergenic food. He says, "Anything to be sociable," but at a later date is able to punish his hostess exquisitely by telling her, "You know, my dear, the other night your food made me very sick!"

Sometimes grown-up "men" (more rarely, women) will eat allergenic foods because their aging mothers say: "Don't listen to the doctor, Mother knows best. Eat everything! No good food ever hurt anybody!" These grown-up children listen to mother, and have their allergic illness, and continue eating allergenic food in spite of medical advice interdicting the use of this food. The offending food will continue to be eaten until the patient can resolve his ambivalent feelings toward medical therapy and forget his persuasive mother's urgings and learn to accept the necessity of following the advice of the allergist, who is symbolically the threatening stern father figure or father substitute in the patient's unconscious thinking.

Sometimes an offending food is eaten as symbolic resistance to the authority of a restrictive parent-surrogate, the allergist. This behavior is most prominent when the patient first learns the nature of his illness and the identity of the allergenic foods. In general, the patient with food allergies dates his illness from the moment his doctor restricts his diet—and not from the time that he first noticed his troublesome (allergic) symptoms. The patient in this category often develops unconscious anxiety and fear from interdiction and deprivation of foods (particularly favorite foods) by the authoritarian figure, the allergist. (However, a few patients with excessive guilt feelings welcome dietary restrictions as symbolic and real punishment for their real or imagined misdeeds, and have through self-abnegation relief from some of their basic anxiety and guilt).

Patients defying the authority of the allergist often think: "Who says I can't eat this? I'll show him, all right!" The therapeutic dilemma results when a patient wants to be helped and at the same time seems unable to change his unconsciously hostile attitude toward his doctor. Such patients alternately obey and disobey the physician's directives until psychotherapy

has enabled them to lose their ambivalence and to develop a more appropriate sense of reality function with respect to the doctor and his advice. Interestingly enough, such a patient may initially "yes" the allergist, and take great pains to assure his doctor that his instructions will be followed to the letter—but the clinical behavior of such a patient consistently shows great resistance and unconscious hostility against carrying out any constructive recommendations made by the physician. Sometimes resistance to the physician's suggested therapeutic program conceals strong dependent needs of the patient, who may seek unconsciously to secure excessive parent-like attention from his doctor in the form of scoldings for defections or exhortations urging the patient to do what is good for himself through abstinence from allergenic foods.

Then, there is a group of individuals who categorically find it impossible to believe that a given wholesome food can cause their clinical symptoms—and even though such a patient is relieved by a temporary elimination of offending foods, he will insist on eating them. This is particularly true of the patient with paranoid trends who unconsciously hates and fears everybody because he projects his own hostility onto others.[3,18,30] He feels that everyone is out to mistreat him in one way or another and that the physician's only goal has been to discommode him unnecessarily by making his daily life more difficult by the interdiction of the use of specific, often favorite, foods. Such patients often find it much easier to believe that someone has been poisoning their food than that the food itself has allergenic properties as far as they are concerned.[1] This is because they can admit of no defect in themselves, not even an allergic one.

Often, people who need to make important decisions and bear the full consequences of these will drink milk, which is a known allergenic substance for them. In such instances, it seems that milk-taking represents a craving for the dependent status they once had, where some strong authoritarian figure took full responsibility for making all important decisions. Thus the patient babies himself by eating lightly, partaking of much milk and milk-containing foods, and may end by being babied by his family because he has a self-induced allergic illness. The eating of security foods and more particularly reward foods resembles any other type of self-indulgence which is tinged with auto-eroticism.

Sometimes patients have a conscious (more often, an unconscious) need to be sick, and this can most easily be satisfied by eating a symptom-producing allergenic food. Sometimes a person may acquire his much-desired, passive-dependent role through allergic sickness. Sometimes he can get the extra attention he craves from his family only through allergic illness. Sometimes he can dominate his family, friends and business associates by getting them to be sorry for him because of his allergic illness, and to grant him special concessions, however unreasonable these may be. Often a woman punishes her husband and family through self-induced allergic illness which creates increased expenses and inconveniences. Sometimes

self-induced allergic illness provides the route of escape from burdensome household, marital and business responsibilities. In mild depressions, self-induced allergic illness often is symbolic as well as very real punishment which the patient inflicts on himself for real or imagined wrongdoing and in this way temporarily lessens his basic guilt reaction and anxiety and decreases the intensity of his depression. In more severely depressed individuals, self-induced allergic illness symbolically may represent self-mutilation or self-destruction. Persons in this category who develop allergic hives or allergic dermatitis often scratch themselves until they have numerous excoriations before they have significant relief from their depression. In most of these individuals, an allergic skin reaction seems to be an essential factor which initiates the scratching behavior.[6,15,27] These persons seem to need, in addition to their self-induced allergic illness, some external signs which advertise their extreme physical suffering. Sometimes the ingestion of a known allergenic food permits a patient to vent his latent hostility against the person who urged him to eat the offending food: "You made me sick. You knew I should never eat chocolate. I hate you!"

A patient can get tired of his new diet, particularly the rotary diet,[20] even though it keeps him free from allergic illness. Rather than longing for any special food, the patient may long for the formerly satisfactory, familiar pattern of eating. He feels he must return to the "orange juice, eggs, toast and coffee" breakfast as an everyday event, even though such a menu will induce allergic illness. This trend is especially strong in persons with obsessive-compulsive behavior patterns, who seem to get more comfort from repeating an old familiar pattern of eating than discomfort from ensuing allergic illness.

Occasionally, persons with severe fixed food allergies abstain from ingesting offending food for many years; then, having genuinely forgotten that they should not eat the allergenic food, they eat it and get acute and often severe allergic illness. Thereupon, there is strong psychological reenforcement of apparently forgotten memories and patterns of behavior, so that once more, often for many years, they will not ingest the offending food. This pattern of behavior has some resemblance to extinction through disuse of a conditioned reflex pattern of behavior which can be reinstated and re-enforced through once more experiencing a strong noxious conditioning stimulus—in this instance, the severe allergic reaction.[24,29]

Often the excessively thrifty housewife may not be able to throw away any left-over food. Even though it may give her an allergic illness to do so, she will eat it. Not infrequently, such a woman refers to herself as "the human garbage pail." This patient is often unattractively obese. She feels, and often is, rejected by her husband. Symbolically, the eating of left-over foods obscurely suggests that she is fit only to have the "left-over" love of her spouse. Sometimes the allergist can get the patient's husband to be a little more attentive to the emotional needs of the wife. When this

is done, the wife may no longer have the driving emotional need to eat excessive amounts of food or left-overs.

Occasionally a female patient will eat an allergenic food to punish her doctor: "You haven't helped me a bit. See how sick I am." Inquiry will show that the patient ate the offending food after her husband had complained of the cost of her medical care, implying that she wasn't worth the cost of the treatment. The patient in her anger then eats the offending food, has her allergic illness, and in this way attempts to punish her allergist.[4]

I have noticed that patients who experience a sudden episode of repressed anger or resentment often are likely to eat allergenic foods as if to punish themselves for their own feelings, particularly where such negative feelings are directed at some person whom they should love, admire or respect.[29,30,31] Some psychiatrists and psychiatrically oriented allergists seem to believe that such reactions are largely psychosomatic ones and that antigen-antibody allergic reactions play no part in such reactions. However, there are many instances where clinically we see that if the patient is emotionally serene and eats an allergenic food, he experiences an allergic illness which can be characterized clinically with respect to duration, intensity, rate of evolution, and regression of signs and symptoms. Similarly, we see in the same patient episodes of repressed anger and resentment when he has eaten no allergenic food; and clinically we can describe the psychogenically induced psychosomatic response. However, when the patient is emotionally disturbed in this special way and eats the allergenic food, the total reaction seems greater than could be accounted for on the basis of arithmetic summation of both allergic and psychogenic reactions, as judged by clinical criteria alone.[19,22]

It is well known today that persons experiencing an acute episode of repressed anger or resentment have prompt changes in the function and structure of gastric mucous membrane and other structures. There is during such a state of repressed anger, great hyperemia of the lining of the stomach, and increased volume flow of blood to the organ. Additionally, there are alterations in secretory function. It seems probable that much more antigenic food material might penetrate the gastric mucous membrane-vascular barrier under these conditions per unit time than when the stomach lining is under basal conditions when the patient is emotionally serene.[31] Under these circumstances, therefore, it should be possible for a huge amount of food antigen to suddenly flood the circulation immediately postprandially.[26] This alone could account for the more severe allergic reaction in a person eating the offending food when he is emotionally disturbed, since it would provide a higher blood concentration of food-antigen for reaction with the tissue antibody. Where the skin is the allergic shock organ, repressed rage and resentment also cause an increase in the volume flow of blood to the skin, thus making it possible to bring more antigen material per unit time to react with fixed cellular antibodies than would be

possible if the patient eating the offending foods were in a serene state of mind. I suggest this theoretical formulation based in part on well-established physiological observations, since it indicates that a facilitation of an allergic reaction following ingestion of an offending food by an emotionally disturbed person who represses his feelings of anger and hostility could still be explained on the basis of an antibody-antigen union in the shock organ.[6,7,9,30]

This formulation does not imply that the simultaneously occurring psychosomatic reaction triggered off by repressed anger or hostility cannot of itself also cause clinically evident psychosomatic signs and symptoms.[6] As methods are developed for quantitation of food antigens in circulating blood,[11,12] there is hope that these theoretical considerations will be confirmed by properly designed experiments.

Next, I want to discuss the patients who become curious to learn what would happen if they ate the offending food. These are usually patients who no longer experience allergic illness because they have abstained from the offending food for long periods of time. To satisfy their curiosity, they eat the food. If they develop their usual allergic illness in response to this their curiosity is satisfied, and for some time to come, they have no special need to repeat the noxious experience.

However, if a patient is hyposensitized sufficiently through abstinence so that ingestion of a specific food is not followed by a clinically obvious allergic reaction, he assumes erroneously that he can now eat the food without fear of consequent allergic illness. Often he tends to eat it frequently and in large amounts, as if to make up for lost time—and as a result, tends to lose much of his acquired tolerance for the particular food. When such a patient develops intermittent or steady-state allergic reactions, he usually is unable to detect any correlation between his eating the interdicted food and his troublesome symptoms. Such patients conclude erroneously that their allergist was all wrong about their having had food allergies in the first instance and often proceed to get medical advice elsewhere. If they do return to their original allergist, many such patients always seem amazed when clinical trials once more show that the foods presently causing their illness are the very foods which initially caused them to be sick —and that the elimination of such foods again prevents allergic illness from this source.

Lastly, a very important reason why people eat allergenic foods is that they receive free advice from other doctors (usually surgeons or obstetricians) in a social setting—and sometimes even in a professional setting.

The patient may say, "I'm being treated by Dr. X, the allergist. He has forbidden me to use orange juice and milk."

The surgeon or obstetrician looks sympathetically at the woman. He shakes his head wonderingly and says something like this: "These allergists . . ." and sooner or later the rest follows: "If you want my advice, eat everything. Then you'll be healthy. I personally don't believe in these

allergies." Now, for reasons that are difficult for me to understand, patients feel that a physician giving advice about medical matters without charging a fee has only their best interests at heart—and they eat the allergenic food, get sick, and even begin to believe that their allergic ailment is not induced by foods.

Having reviewed the most frequent causes of food-induced, self-inflicted allergic illness, what can be done to prevent recurrences of such needless sickness? I am making the following suggestions which have proved useful.

A frequent cause of a patient's dietary indiscretions is too-infrequent visits to his allergist. In the management of many patients who have food allergies, it is necessary to see them regularly at four to eight week intervals after they have become asymptomatic and to review their health status and reiterate therapeutic suggestions previously made. Patients are grateful for the doctor's interest and on the whole tend to be much better controlled allergically and emotionally than would otherwise be possible. Thus, the patient becomes a little more impervious to the free advice showered upon him by others.

I have indicated that people who are allergic to certain foods, as proved by clinical study and testing, often eat such foods, knowing consciously or unconsciously that they will be sick. What can the allergist do to help prevent such episodes?

First, the allergist must understand that the patient as a human being has the emotional right to resent and reject any program of therapy (food restriction) which changes his usual pattern of eating behavior and which carries with it the implication of physiological inferiority. Don't expect mere logic to govern the conduct of the allergic patient, particularly when the logical and emotional needs of the patient are divergent.

Don't expect the patient to comply immediately with even reasonable requests, especially if he has paranoid, obsessive-compulsive, or depressive behavioral trends. (Don't think that all people with such patterns of behavior are institutionalized—many are useful citizens, and even leaders in the community when their emotional aberrations are harnessed in ways approved by society). Don't take the rejection of your authority as a physician and as a specialist in allergy as a personal affront—the patient would reject the same advice concerning food restrictions no matter who the doctor was that gave it. Don't say nasty things about the surgeon or obstetrician who interfered with your program of allergic therapy through his unconscious need to show your patient that he too is a medical authority. Talk to your confrère and let him know how he interfered with your practice and with the best interests of your patient—and if you have proof of continuing interference from the same source, take it up with the county medical society officials for adjudication. Allergists have suffered too much from this type of professional sniping—and allergic patients even more.

The allergist should recognize that the treatment of a patient with food

allergies is an educational program that must proceed continuously with short-term and long-term goals. The allergist and his patient are learning together to overcome allergic illnesses. There is no such thing as routine treatment of patients with food allergies; each case needs individual management. The allergist in his zeal as a doctor may want his patient to enjoy immediately the best possible health through elimination of known allergenic foods—but the patient may not be emotionally ready for good health. If this is true—as it often is—the allergist must help the patient through supportive and reconstructive psychotherapy to regain sufficient emotional resources to face his life problems as they become increasingly difficult, without needing to escape the sense of personal responsibility by fleeing into self-induced allergic and emotional illness. The patient will need time, and often a great deal of time, before he can alter his mode of adaptation to threatening life situations.

The allergist should see his patient often enough so that the patient does not feel neglected—but not so often that the patient becomes entirely dependent on him. Let the patient talk himself out and gain relief from this source, and learn to guide the patient gradually to insights which he must attain if he is to be freed from his former emotional need to inflict repetitively self-injuring, self-induced allergic illness on himself.

If the patient has gone through an episode of such illness, the allergist should not scold him. It is much better to be permissive, "Yes, it was all right for you to have done that—but now that you've learned from this allergic illness, let's not have it happen again until I ask you to eat that food for testing purposes." Persons who are quite immature emotionally cannot be handled in this way. Instead, it is necessary for the physician to be harsh and verbally punitive before the patient will conform. This is analogous to the spanking a fond parent gives his naughty child.

It is of value to alert the patient to the relationship between emotional stress and the craving for certain classes of food. It is necessary to help the patient meet his emotional problems realistically so that he will not have the symbolic need to eat reward, security, or pleasurable-association foods, which will surely make him sick. The patient who cannot say "no" to his hostess cannot say "no" under other appropriate circumstances, and must be given supportive psychotherapy so that he can become more aggressive and dominant in his relations with other people. The patient must be prepared not to allow his mother, or other doctors, to interfere with therapy suggested by his allergist.

It is wise at the very beginning of treatment of a patient with food allergies to set up a tentative schedule for retesting the patient's clinical sensitivity to the interdicted foods—so that the patient will be able to look forward with anticipation to these trials. As a result he will be much less likely to feel that elimination of offending foods from his diet was an arbitrary and unnecessarily cruel procedure. Very few patients are tempted to "jump the gun" and eat the offending food before the time actually set for clinical testing. Such retesting may indicate that the patient is sufficiently

hyposensitized so that he can eat the formerly offending food once or twice a month without clinically obvious allergic symptoms—and if this is so, the patient will get an enormous psychological lift from his newly acquired tolerance for a formerly allergenic food. However, when a food of this sort is re-introduced into the patient's diet, it should be understood that if allergic symptoms recur from its use, then it must again be eliminated from the patient's diet.

The allergist must constantly emphasize the dynamic nature of food allergy, and how concomitant factors such as pollinosis, bacterial infections, or intercurrent illness may alter food tolerances. The doctor must try to get the patient to establish new, therapeutically valid patterns of eating so firmly that they become second nature to him. The allergist should permit the patient to get relief from confessing that he has eaten forbidden foods. At such times, it is wise not to become angry with the patient and give him verbal evidence of such feelings, since an understanding attitude on the part of the physician at such a time may be the turning point in the successful treatment of the patient who has repeatedly resorted to self-inflicted food-induced allergic illness as an emotional mode of behavior. The allergist should be permissive and understanding—but at the same time firmly insistent on what he knows to be right.

In general, the less a patient is ordered to follow a fixed regimen of eating, the better it will be all around. Dietary changes should be suggested, not commanded. The chief exception is with the excessively dependent patient who early in treatment will need harsh restrictions—symbolically like those once given by the patient's dominant parent. The allergist must remember that allergies to food can cause primary allergic mental syndromes and secondary reaction patterns of behavior which can be resolved only when the offending food is eliminated from the patient's diet, while at the same time the patient receives psychotherapy.[28] A patient suffering from food allergies may at the same time be suffering from a serious primary mental illness. Such a patient requires expert psychotherapy along with allergic therapy, and especially in this case the allergist's therapeutic suggestions and instructions must be couched in terms and in suggested behavioral patterns which will be acceptable to the patient who is mentally ill. The allergist can become sufficiently expert in psychotherapy to do a good job if he is interested in this aspect of treatment—but if he is not, he can achieve good results through the formation of a close working association with a psychiatrist who will co-operate in working to aid the patient's progress toward recovery from both the allergic and the mental illness.

Every person suffering from food allergies is a reactive individual who is sick—and the patient's food-induced allergic illness, which is so important to the allergist, may be merely one of the smallest problems that the patient suffers from, from his own point of view. The allergist should help his patient overcome the illness which allergenic foods induce—but he should not stop there.

Help the patient in every way that you, the physician, allergist, healer, can; and in time you will have a patient who no longer has the urgent need to experience repetitively self-inflicted, food-induced allergic illness.

SUMMARY

This paper analyzes some of the reasons why patients who are allergic to specific foods, as proved by clinical testing, deliberately eat such foods, thus creating self-inflicted, food-induced allergic illness.

An individual's patterns of choosing and eating foods become psychologically highly structured, conditioned reactions. Foods have emotional values for an individual over and above the hunger-satisfying capacity of all foods. Some foods are "gustatory pleasure" foods, "pleasurable association" foods, "security" foods, "reward" foods, "fetish" foods, et cetera. The patient's urgent need for ingesting foods in the above categories in times of stress may be so great that the emotional support derived from eating them far outweighs the consequences of self-inflicted, food-induced allergic illness.

Sometimes a patient genuinely forgets that he is not supposed to eat the allergenic food; sometimes, after a period of abstinence from the food he is merely curious to see if eating the food will make him sick. Sometimes suggestions of his family, friends, or other physicians outweigh the recommendations of the allergist. Sometimes a patient who has severe guilt feelings or is depressed, or wants special attention or special privileges from others, may experience strong drives to eat allergenic foods until he is quite sick.

A tentative explanation is offered for the increased severity of self-inflicted, food-induced allergic reactions in individuals who are experiencing an acute episode of repressed anger or resentment at the time of ingestion of the allergenic food. This explanation is given in terms of what is known about the physiology of this type of psychosomatic reaction and in terms of the cellular antigen-antibody reaction. Undoubtedly, the situation is more complex than indicated by this initial formulation.

The allergist, by understanding that changing eating habits constitutes a severe dislocation in the patient's ordinary way of living, can help the patient by rendering supportive and reconstructive psychotherapy, and in this way can help the patient to make a better adjustment to the stresses of his life and to the necessities of allergic treatment. The allergist must see his patient at sufficiently frequent intervals to give him the approval he desires and to reiterate therapeutic suggestions about allergic management.

The allergist should suggest definite times of retesting the patient's tolerance for allergenic foods; this reduces the patient's curiosity to try eating the food whenever he chooses. If the patient admits to having eaten an offending food, the allergist should be kindly but at the same time insistent that the patient follow the therapeutic program.

The allergist must treat his patient as a whole person, recognizing that the patient's food-induced, allergic illness may be the smallest part of the

patient's life problems from the patient's viewpoint. As the allergist is able to help the patient develop more appropriate and mature adaptations to his life problems (including his allergic problems), the patient will be less inclined to resort to self-inflicted, food-induced allergic illness as a method of solving his pressing emotional problems.

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EFFECT OF THEPHORIN UPON PRIMARY DYSMENORRHEA

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THE present-day treatment of primary dysmenorrhea runs the gamut from the administration of simple sedatives, analgesics, and antispasmodics through alcohol, amphetamine, hormone medications, exercises, and psychotherapy to various minor and major surgical operations, including, as a final resort, presacral sympathectomy, a formidable procedure not always unattended by serious postsurgical complications. It is the purpose of this report to call attention to a therapeutic agent which, over a two-year period of observation, has shown promise in satisfactorily controlling the distress of essential dysmenorrhea.

Macpherson[2] and Hoffman[1] successfully relieved dysmenorrhea by prescribing an antihistaminic medication to be taken before the menstrual period. Herein are presented twenty additional cases of primary dysmenorrhea which were beneficially influenced by the administration of an antihistaminic preparation.

Twenty females, whose ages ranged from thirteen to forty-two years, were studied. Sixteen were single and four married. The latter were multiparous; one was a grandmother. In the married patients the dysmenorrhea, which was severe, had continued unabated despite their deliveries. Nineteen had a positive personal history of allergy manifested by bronchial asthma, hay fever, perennial allergic coryza, eczema, urticaria, and angioneurotic edema. Four of these patients also had a positive family history of allergy. Three patients exhibited allergic manifestations prior to the onset of the menarche. The remaining patient had a negative history of allergy.

The pain characteristically made its appearance with the first menstrual flow or early in the menarche, occurred with each period, was crampy and often severe, began just prior to or with the commencement of the flow, and lasted from one to two days. Pathologic causes of dysmenorrhea, such as local inflammatory conditions, cysts and tumors, uterine displacement, endometriosis, and genital hypoplasia, with or without other endocrine stigmata, were excluded.

MEDICATION

Thephorin* (2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindine hydrogen tartrate) was the antihistaminic preparation selected for our study. In contrast to some other antihistaminic agents with a rather high sedative

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quotient which produce drowsiness as a side effect, Thephorin, with its low sedative quotient, more often causes insomnia and jitteriness. Also, side reactions to Thephorin are less pronounced and less frequent. These factors were considered highly pertinent because, for the purpose of our study, it was deemed advisable to obtain relief primarily through an antihistaminic action and antispasmodic effect, if any, rather than through a deep sedative effect which, in turn, would perhaps disrupt normal routine or prove hazardous for the patient.

A 25 mg tablet of Thephorin was administered with the onset of the pain. If satisfactory relief was not obtained, this dose was repeated from one-half hour or one to two hours. When further medication was found necessary, a similar dose was given as indicated every four hours. Usually the first two doses completely eliminated all menstrual pain for the duration of the period.

Side reactions were inconsequential with this regimen. Fleeting jitteriness was noted occasionally but not constantly in the same person. Fatigue and numbness were observed in one patient who, when beginning the treatment, misunderstood her instructions and took the first two doses simultaneously. Subsequent administrations, properly timed, produced no ill effects.

Initially for two months in four patients stilbestrol, 5 mg orally twice daily, was given for twenty days premenstrually to produce an anovulatory period with the absence of pain while Thephorin was administered as described beginning with the onset of the flow; subsequently Thephorin alone produced equally excellent results.

Clinical observations were made over a period of two years. During this time, in order to test the efficacy of the antihistaminic medication, each patient received placebos, which were interpolated now and then at strategic intervals. The administration schedule remained the same. On such occasions, the placebos were strikingly ineffective and the dysmenorrhea was not relieved despite additional doses of placebo medication. The following month, when Thephorin again was administered, the symptoms were completely controlled.

The nature of the flow was not affected by antihistaminic therapy. The duration, amount, color, and rate remained essentially unchanged. Only one patient thought that she flowed more freely or had a "gush" flow during the first day or two.

CASE REPORTS

The following case reports have been selected as being illustrative of the effect of Thephorin upon primary dysmenorrhea.

Case 1.—A. M., forty-two years of age, is married, has two children and is a grandmother. Eczema was present during childhood. At thirty-nine she developed hay fever and perennial allergic coryza. Menarche started at age twelve. Since

then, her periods have always been associated with severe pain. Despite two deliveries, her dysmenorrheic symptoms continued. She always took Anacin or Midol, either separately or in combination, and required three or four tablets daily the first two days. Occasionally, the pain was severe enough to warrant bed rest. Her dysmenorrhea has been completely relieved each month by two Thephorin tablets, 25 mg at the onset of pain and 25 mg one hour later.

Case 3.—E. H., aged twenty-two years, is single, has mild eczema and also presents a strongly positive family history of allergy. Her mother and sister have hay fever. A maternal uncle died of bronchial asthma. Since the inception of her menstrual cycle, her periods have always been painful. During her period she felt tired, desired bed rest, and required four or five tablets of either aspirin or Empirin Compound daily for the first three days. These resulted in only partial relief. Two 25 mg Thephorin tablets, taken monthly, one with the onset of pain and the other one hour later, produced excellent results. She had no pain, did not feel tired, and required no bed rest. She thought that she flowed more freely and had a "gush" flow during the first day or two.

Case 4.—L. A., aged twenty years, is single and has hay fever and a positive family history of allergy, a sister having hay fever. Dysmenorrhea has been present from the beginning of her periods. During the past four years the pain has increased in severity, only partially responding to Midol, Anacin, and hot drinks. Often on the first day a rest of several hours was required and, though lying down, she was quite restless. Two tablets of Thephorin dramatically relieved her pain each month, and she was able to work long and hard without interruption.

Case 8.—C. L., aged thirty-nine years, is married and has had two full-term deliveries. Her family and personal history was negative for allergy. Dysmenorrhea began with her first period. Aspirin, Anacin or Midol, taken either separately or in combination, did not produce satisfactory results. The pain lasted for about two days and often was severe enough to necessitate bed rest. One 25 mg tablet of Thephorin taken at the onset of pain and repeated again about one hour later satisfactorily relieved her symptoms each month.

COMMENT

It is not within the province of this report to establish the pharmacodynamics by which an antihistaminic preparation relieved the subjective distress of primary dysmenorrhea, for it is well recognized that antihistaminic agents also exhibit a sedative and antispasmodic effect. Nevertheless, the prompt and sustained symptomatic relief was interesting. In this small group of patients the response to Thephorin was gratifying, and it appeared significant that whereas in years past their dysmenorrheic symptoms were only partially or inadequately relieved by the usual sedatives and antispasmodics, yet they are now satisfactorily relieved by an antihistaminic agent.

Thephorin therapy for symptomatic relief in primary dysmenorrhea appears to be safe, practical, convenient, and economical. It gives prompt and effective relief, can be taken orally, is attended by minimal and inconsequential side reactions, improves morale, and allows a continuance of normal activities.

SUMMARY AND CONCLUSIONS

Four cases of primary dysmenorrhea, chosen from twenty studied, are presented. All twenty were relieved by the administration of an antihistaminic drug. The encouraging results obtained in this small group of patients warrant further investigation.

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PHENERGAN HYDROCHLORIDE—A NEW ANTIHISTAMINE

A Clinical Report

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IN the treatment of allergic disease, the primary aim is either to eliminate the causative allergens from the patient's environment and daily routine, or to proceed with a hyposensitization program that will stimulate a substantial immunity to the offending substances. However, it is not always possible or practical immediately to carry out definitive measures. Until such time as desensitization therapy is feasible, the patient deserves every effort on the part of the physician to alleviate the allergic symptoms. To date, administration of antihistaminic agents offers the most effective method of palliation.

Phenergan* hydrochoride, a phenothiazine derivative and one of the most potent antihistamines known at the present time,[4,5,6,11,12,13,14,15] is a compound of high potency, with powerful pharmacologic action and more prolonged effect[4,5,6,7,15] than most of the histamine antagonists in common use. Pronounced by Halpern[15] the most active of the synthetic antihistamine preparations, it has been demonstrated[4,6,7,14,15] that Phenergan will protect guinea pigs against 1,500 lethal doses of histamine, and "0.1 mg per kilogram is enough to protect this animal against fatal anaphylactic shock."[4] Halpern concluded that Phenergan "possesses in addition to its remarkable antihistaminic properties, an antianaphylactic activity greater than that of the antihistamines so far studied."[4]

This report deals with the clinical results obtained with Phenergan hydrochloride in symptomatic treatment of 216 patients, twenty-seven months to eighty-four years old. The allergic syndromes presented, the number of patients affected by each, and the results obtained with Phenergan therapy are shown in Table I. Antihistamine therapy was carried out concomitantly with hyposensitization whenever possible.

One hundred and two patients of the entire series suffered from pollen hay fever. In each, a history suggesting sensitivity to grass, tree or ragweed pollens, singly or in various combinations, had been substantiated by intradermal tests. In thirty-seven patients a diagnosis of vasomotor rhinitis had been confirmed by intracutaneous tests, and in seven additional

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*Phenergan® hydrochloride, N-(2'-dimethylamino-2'-methyl) ethyl phenothiazine hydrochloride, was supplied by Wyeth, Incorporated.

TABLE I. THERAPEUTIC RESPONSE TO PHENERGAN

Diagnosis	No. of Cases	Male	Female	Results				
				Dramatic, Excellent or Good Relief	Fair Relief	Questionable or No Relief	Total Patients Benefited %	Failures %
1. Hay fever induced by tree, grass or ragweed sensitivity. Diagnosis confirmed by intradermal testing.	102	56	46	90	4	8	92.16	7.84
2. Vasomotor rhinitis, confirmed positive intradermal tests.	37	17	20	34	1	2	94.59	5.41
3. Vasomotor rhinitis, allergic history not confirmed by intradermal tests.	7	5	2	3	2	2	71.43	28.57
4. Allergic asthmatic bronchitis with hay fever or vasomotor rhinitis or both, confirmed by diagnostic tests.	19	12	7	11	5	3	84.21	15.79
5. Atopic eczema.	5	3	2	2	2	1	80.00	20.00
6. Migraine, confirmed by positive intradermal tests.	3	2	1	2	0	1	66.67	33.33
7. Neurodermatitis.	5	2	3	1	3	1	80.00	20.00
8. Pollen eczema.	3	3	0	1	2	0	100.00	0.00
9. Plant contact eczema.	7	6	1	3	3	1	85.71	14.29
10. Angioedema with hives.	6	3	3	3	2	1	83.33	16.67
11. Contact dermatitis.	7	3	4	1	3	3	57.14	42.86
12. Drug sensitivity							85.77	14.23
(a) Drugs taken by mouth	6	4	2	4	1	1	83.33	16.67
(b) Drugs taken by injection, particularly penicillin.	8	6	2	6	1	1	87.50	12.50
13. Allergic purpura.	1	0	1	1	0	0	100.00	0.00
Totals	216	122	94	162	29	25	88.42	11.56

cases the history was suggestive of vasomotor rhinitis, but diagnosis could not be confirmed by skin testing.

In nineteen cases an allergic asthmatic bronchitis occurred secondary to pollen hay fever or vasomotor rhinitis, as confirmed by history of allergy and positive diagnostic tests.

Included in this series were five cases of atopic eczema, three cases of eczema provoked by pollens, seven cases of contact dermatitis caused by plants, and seven cases of contact dermatitis induced by cosmetics or industrial irritants.

Five cases of neurodermatitis, six cases of angioedema with hives, three cases of allergic migraine confirmed by history and diagnostic tests, and one case of allergic purpura also were treated with Phenergan.

The fourteen cases of drug sensitivity included six patients whose symptoms followed ingestion of a drug and eight whose allergic manifestations were induced by injection of penicillin.

DOSAGE

The adult patients received a total daily dosage of 37.5 mg Phenergan hydrochloride, administered in three doses of one 12.5 mg tablet each, first taken after breakfast and repeated in midafternoon and again before retiring. For children, one half this dose was used. It was observed, however, that the full adult dose could be administered to children if required to control symptoms.

The patients suffering from allergic asthmatic bronchitis secondary to hay fever or vasomotor rhinitis were treated with a tablet containing 12.5 mg Phenergan and 3/8 grain ephedrine.

RESULTS

The subjective and objective improvement achieved in these patients by treatment with Phenergan exceeded by far the results obtained in both clinical trials and experimental studies, with any other antihistamine.[10] Phenergan relieved symptoms within one-half hour in practically all patients who responded, and relief could be maintained indefinitely on continuous dosage. Single doses were effective for periods of four to twenty-four hours. No other antihistamine, in our experience, has exhibited such prolonged action.

In the entire series of 216 cases, significant benefit was obtained in 191 (88.42 per cent). Patients were classified according to: (1) Objective findings, e.g., shrinking of the boggy intranasal membrane in vasomotor rhinitis, with return to a more natural color; alleviation of dermatosis, with disappearance of vesicles; elimination or reduction of the musical râles that characterize pollen asthma. (2) Response to searching questions as to subjective evidences of improvement. All patients were encouraged to minimize the relief they experienced and urged to weigh carefully their estimate of improvement obtained, so that in no instance would the reports be overenthusiastic. It is realized, of course, that since there is no scientific yardstick for measuring subjective symptoms, calculation of subjective improvement presents inherent difficulties. Every effort was made in this study, however, to arrive at an accurate interpretation of the alteration in the condition of each patient. Objective findings were correlated with the reported extent of subjective relief, and the results were recorded as (1) dramatic, (2) excellent or good, (3) fair, and (4) questionable or no relief.

1. The result was classified as "dramatic relief" if objective evidence of allergy had completely disappeared and the patient was free of all discomfort.

2. If objective manifestations of allergy showed a definite improvement and subjective symptoms were reported as diminished, so that the patient could be considered to have 80 per cent benefit or more, the result was interpreted as "excellent" or "good," according to the degree of relief obtained. Patients in this category would state, for example, "I am not completely free of all my symptoms, but practically all are gone, and what remain are not severe."

Of the entire series, 75 per cent of patients experienced "good" to "dramatic" relief; that is, they were freed of 80 to 100 per cent of allergic symptoms.

3. Twenty-nine patients (13.42 per cent) reported that Phenergan afforded only fair control of the allergic complaints.

4. In some cases another antihistamine was administered for comparison when Phenergan produced less than 80 per cent improvement. If the second preparation provided a greater degree of benefit, the case was classified as a failure for Phenergan, and recorded as "questionable or no relief," despite the fact that symptoms had been controlled to some extent. Twenty-five patients (11.58 per cent) were included in this category.

Of the 102 patients suffering from hay fever (sensitivity to grass, tree or ragweed pollens), ninety-four (92.16 per cent) were benefited by Phenergan therapy. In our experience, results obtained with Phenergan in symptomatic relief of pollen hay fever were far superior to those obtained with any other antihistaminic agent.

In the thirty-seven patients with proved vasomotor rhinitis, thirty-five (94.59 per cent) were relieved, thirty-four of them to a marked degree; whereas, of the seven patients in whom an allergic basis for vasomotor rhinitis could not be proved, 71.43 per cent were improved.

Phenergan was satisfactory in 84.21 per cent for the treatment of allergic asthmatic bronchitis secondary to hay fever or vasomotor rhinitis. The addition of ephedrine to the 12.5 mg tablet administered to these patients should enhance the effectiveness of Phenergan treatment. Further results on this phase of the study, which is still in the investigative stage, will be reported later.

Phenergan was 100 per cent effective in patients with pollen eczema, and relieved 85.71 per cent of those with plant contact dermatitis, but only 57.14 per cent of those with contact dermatitis caused by cosmetics or industrial irritants responded satisfactorily. Of the patients with atopic eczema, 80 per cent responded, as did those with neurodermatitis. Angioedema with hives was controlled in 83.33 per cent of cases. (Other workers, however, have reported Phenergan 90 to 100 per cent effective for angioedema and urticaria). In fourteen cases of drug sensitivity, Phenergan therapy elicited a satisfactory response in 85.77 per cent. The one patient with allergic purpura responded well, and two of the three patients with allergic migraine were likewise benefited by Phenergan. It is realized, of course, that in small groups of cases one response or failure can alter the statistics significantly.

TOXICITY

Of the 216 patients treated with Phenergan, only 12 per cent experienced side effects, and only three patients (0.014 per cent) found it necessary to discontinue medication. It was gratifying to find that an antihistamine so potent and possessing such high therapeutic value as Phenergan produces so few untoward symptoms. This is particularly noteworthy, since with most antihistamines if the toxicity of the compound is reduced, the

efficiency is likewise lowered. In contrast, however, Phenergan manifested superior therapeutic properties, with absence or infrequency of side actions.

In the use of Phenergan for children, observations in this series confirmed those of Peshkin and associates,[8] who, in reporting on private and clinic patients, stated that side effects were 20 per cent less frequent in children on the dosage recommended for adults than in adults on the same schedule.

The most common side reaction was drowsiness, although an occasional patient reported nervousness; nausea and dizziness occurred in some instances. Patients who experienced pronounced drowsiness could take the combination of Phenergan and ephedrine with fewer untoward effects.

The mild sedation produced by Phenergan in some patients (but rarely to the point of disability) is distinctly beneficial in many cases of allergic disease. It is both simple and practical to determine the sensitivity of the individual patient to the sedative action of Phenergan, and to regulate his dosage schedule accordingly.

DISCUSSION

The pharmacologic mechanism of Phenergan appears not to be entirely explainable on the basis of antihistaminic action alone.[8] Halpern[4,5,6] suggests, on the strength of his experimental findings, that Phenergan acts by stimulating capillary resistance to the permeability produced by histamine and histamine-like substances.

Phenergan neutralized the action of histamine on smooth muscle, the intestine and the vascular system in animals,[4,6,7] and prevented or corrected the effect of histamine on arterial pressure in the dog, cat and rabbit.[6] In the experiments of Vallery-Radot and co-workers[13] Phenergan exerted on the vascular walls of animals the most powerful action of all known antihistamines.

In man, small doses of Phenergan suppress skin reactions, direct and indirect.[7,15] Quantitative studies conducted by Vallery-Radot and associates[15] on inhibition of the Prausnitz-Küstner phenomenon demonstrated that Phenergan in less than one-third the dose of the next most effective antihistamine completely suppressed the local passive transfer reaction. Likewise, Phenergan inhibited the Arthus phenomenon in rabbits,[1] whereas other antihistamines failed to modify the local edema and necrosis that characterize this type of allergic response. Phenergan also prevented the Shwartzman reaction with equal effectiveness.[13]

Apart from its action in allergic conditions, Phenergan prevented the development of acute pulmonary edema and orthostatic albuminuria in experimental animals.[5] Two groups of investigators[2,7] were able to forestall, with Phenergan, the appearance of acute pulmonary edema in rabbits that had received intravenous injections of epinephrine. Laboratory animals were similarly protected against pulmonary edema induced by chloropicrin

and phosgene gas.[2,7] In addition, the action of Phenergan as a local anesthetic is four to five times greater than that of cocaine.[7]

Although Phenergan neutralizes the effect of histamine on all other physiologic functions,[12] like other antihistaminic agents it does not inhibit the action of histamine on the gastric mucosa[6,12] nor on gastric secretions.[6,12] In the researches of Vallery-Radot and co-workers[12] on experimental production of ulcer and gastric perforation by histamine in guinea pigs, animals that had been protected against 300 to 400 lethal doses of histamine developed gastric lesions identical to gastric ulcer observed in man. In some of the animals perforation occurred in twenty-four hours to several days, resulting in a fatal peritonitis.

In a clinical trial[16] on sixty-four allergic patients Phenergan was highly satisfactory in hay fever and vasomotor rhinitis, and 94 per cent effective against urticaria and angioedema. Shulman[9] studied the therapeutic action of Phenergan in fifty-five patients who had failed to respond to all other available antihistamines. Fifty-six per cent of this group showed marked improvement to complete relief of symptoms when given a single daily dose ranging from 6.5 to 25 mg. Of ten patients in this series suffering from bronchial asthma associated with vasomotor rhinitis, seven were improved on Phenergan hydrochloride after no results had been obtained with other antihistamines. Similar success was reported by Vallery-Radot's group.[11]

Feinberg[3] also found Phenergan effective in a variety of conditions and observed that it has the additional advantage of prolonged antihistaminic activity; hence he considered that it was most useful for patients in whom a bedtime dose was sufficient to prevent morning symptoms of nasal allergy. In many cases one dose was sufficient.

Against experimental asthma in the guinea pig, Phenergan exhibited a duration of action three times as long as the effect of other antihistamines under the same conditions.[5] Therefore, it is not surprising that in the asthmatic patients of Waldbott and Young[16] Phenergan produced the best results of all the compounds tried; but whether the drug exerted a higher degree of specific action on bronchospasm than the other compounds tested, or whether the improvement resulted from the pronounced soporific effect, the authors were unable to determine. In the opinion of Peshkin and his associates,[8] "the soporific action of Phenergan surpasses that of all other antihistaminic drugs," which for many reasons "makes it an especially desirable antihistaminic."

SUMMARY

Phenergan hydrochloride is a highly effective antihistamine, with action rapid in onset; single doses maintain alleviation of symptoms for periods of four to twenty-four hours. No other antihistamine employed by the author has exhibited such prolonged effect.

In this series of 216 cases, 88.42 per cent of patients were afforded

protracted symptomatic relief, during which time definitive therapy could be carried out. The unusual effectiveness and low toxicity of Phenergan establishes a definite place for it in the armamentarium of the physician.

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ORTHOXINE IN BRONCHIAL ASTHMA

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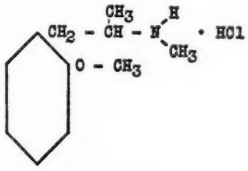
ORTHOXINE (ortho-methoxy-beta-phenyl-isopropyl methylamine hydrochloride) is a sympathomimetic amine which is related in chemical structure to epinephrine. It has the following structural formula:



PHARMACOLOGY AND TOXICOLOGY

In animal and isolated tissue studies Orthoxine has been demonstrated to be an effective bronchodilator and smooth muscle inhibitor.[2] It does not have the pressor and central nervous system stimulating properties of the other chemically similar drugs used in treating asthma. It has been shown that Orthoxine usually has no effect on blood pressure and may even have a transient depressor effect.

Acute and chronic toxicity studies have shown that Orthoxine is no more toxic than ephedrine in experimental animals.

Section I

METHODS

This is a report of the controlled evaluation of Orthoxine* in a selected group of patients seen at the Charity Hospital Out-Patient Allergy Clinics by one of us (L. C.). This section consists of two separate controlled clinical studies done at different times.

In the first study there were twenty-four adult patients with bronchial asthma, no attempt being made to differentiate the types of asthma. Patients were seen in the clinics at weekly intervals for from four to eight weeks and at each clinic visit were given a week's supply of Orthoxine or placebo. Patients were instructed to fill out a mimeographed form each week and to record the time of onset of each attack, its severity, and the duration of symptoms. At each return visit the patient was questioned about the occurrence of side reactions, and the amount of Orthoxine taken during the week was recorded. The forms were then studied, noting the number of hours of mild, moderate, and severe symptoms during the week as interpreted by the patient. In this study a small maintenance dosage of 100 mg three or four times a day was given to twenty of the twenty-four patients, only four patients receiving larger doses.

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*Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

TABLE I. AVERAGE NUMBER OF HOURS OF SYMPTOMS PER PATIENT PER WEEK

Patient	mg/day	Placebo				Orthoxine			
		Wks.	Mild	Mod.	Severe	Wks.	Mild	Mod.	Severe
1	800	2	28.	0	2	2	12.75	0	1
2	800	10	5.16	6.65	14.17	13	4.68	5.65	6.17
3	800	16	2.62	1.66	0.41	6	2.5	7.92	0.25
4	800	2	0	6	4.5	2	0	1.75	0.75
5	800	4	3.75	0	7.75	2	3	0	2
6	800	1	0.25	0.25	0	2	0.62	0.12	0.12
7	800	12	8.08	4.04	20.59	10	13.46	4.3	15.36
8	800	12	28.33	0.04	5.08	8	14.68	0	3.19
9	800	6	2.54	0	1.96	4	4.31	0	5.81
All patients			8.75	2.10	6.27		6.22	2.19	3.85

Although there was a trend to a lesser amount of symptoms while on Orthoxine, these results were not significant, and it was felt that the dosage used was too small. Therefore, a second study of nine asthmatic patients was begun and continued for twenty-four weeks. This second group of nine patients was studied in the same manner as was the first group. This group was instructed to take 200 mg of Orthoxine four times a day, and an additional 200 mg at the onset of an asthmatic attack. The same directions were given for the placebo. It should be pointed out that this above dosage was larger than that which is customarily used. The usual dosage recommended is 50 to 100 mg every three or four hours if needed.

In the second study the total average number of hours of all symptoms on placebo was 154.13, or 17.12 hours per patient per week, and on Orthoxine 110.39, or 12.26 hours per patient. It is not possible to compare hours of mild and severe symptoms in the same patient. Therefore, the decrease in amount of severe symptoms is of definite importance, since these patients might have shown benefit in the lessening of severity of symptoms and not necessarily in the total hours of symptoms. Also, as stated above, the dosage used in the first group was too small.

Dr. Huldah Bancroft, professor of biostatistics, Tulane University School of Medicine, tested the findings and reported that there were no statistically significant differences in the average hours of mild, moderate, or severe symptoms of either group totals while on placebo or on Orthoxine.[1]

The questionable results obtained in the first group in comparison with the good results obtained by other investigators of Orthoxine in bronchial asthma were thought to be due to the lower dosage, and the second study was therefore attempted. Although the actual reduction in the hours of symptoms while under treatment with Orthoxine is greater in the later group, the smaller number of patients studied still makes a conclusive statement impossible. It must be remembered also that the psychic improvement while on Orthoxine would be carried over to some extent while the patient was on placebo. Therefore, possibly the hours of symptoms on placebo would have been greater. The patient, of course, had no way of distinguishing between Orthoxine and placebo. In Section II (below)

Orthoxine was given to a group of patients without the use of a placebo. In a controlled study, as in Section I, the degree of symptoms must be taken into consideration, as it would be faulty to compare hours of severe symptoms with hours of mild symptoms. The severity of symptoms was evaluated by the patients themselves; this, of course, is a subjective evaluation. However, in this study the errors of subjective interpretation were obviously neutralized since both groups were crossed over and because the total hours of all degrees of symptomatology were computed for both groups. If this study were to be continued, and a larger number of patients used, the results would be more definite.

SIDE REACTIONS

In the first group, two of the patients reported nausea and vomiting on one occasion while on Orthoxine, and one patient reported nausea on both Orthoxine and placebo. One patient reported sleepiness while on Orthoxine. These reactions were mild in each case. In the second group one patient reported dizziness, one reported nausea and weakness, and one complained of being sleepy, all while on Orthoxine. However, each symptom was reported on only one occasion. One patient reported dizziness to both Orthoxine and placebo. Other investigators have found that side reactions to Orthoxine have been transient.

Section II

In this portion of the study, private patients were given Orthoxine in an attempt to evaluate its efficacy. This is the usual type of study carried out by other investigators. In this group large doses were used when indicated. Adults and large children were given 100 mg tablets, the dosage ranging from one-half to two tablets (the maximum dose). It was given from one to four times daily or merely when needed. A syrup of Orthoxine (which contained 300 mg per ounce) was used in small children, the dosage varying with the size of the child. A total of forty-five adult patients were studied with the following reported results:

Excellent to good	68.8 per cent
Moderate	22.2 per cent
Poor to none	8.8 per cent

The first two groups combined give a total of 91 per cent benefited. Some patients stated that intervals up to an hour elapsed before relief was obtained. Side reactions were mild and infrequent. Three patients reported drowsiness; however, drowsiness occurred in one of these after the use of many medications. Three patients also reported slight drowsiness. Another complained of some early weakness after taking the medication which did not persist when the medication was continued. One patient complained of nausea, while another complained of vertigo and palpitation. One patient, who had attacks of status asthmaticus, stated that the medicine made her hoarse.

The syrup of Orthoxine was also used in eight children. Four reported good results, while four had moderate results. Therefore, all children had some benefit from Orthoxine.

A group of ten patients were given a tablet containing 50 mg Orthoxine, 100 mg aminophylline, and 0.25 mg hyoscyamine hydrobromide. The dosage ranged from one to two tablets when needed. All of the patients reported good results. No side reactions were observed, except that the same patient who reported drowsiness after all medications again appeared in this group. Six of the patients in this group failed to obtain complete relief on Orthoxine alone. Although this particular combination was effective in this small group, the possibility of side reactions to hyoscyamine in others must be considered.

A two-stage tablet of Orthoxine was used in nine patients, with 100 mg present in the outer coat and 100 mg available for slower absorption. Six patients reported good results, and three reported moderate results. A mixture of Orthoxine, Pyrrolazote and aminophylline was used in seven patients; six reported good effects, while one had moderate results. This mixture was especially suitable for patients who had marked nasal symptoms in addition to asthma. Pyrrolazote is an effective antihistamine.

Suppositories containing Orthoxine 0.2 gm and aminophylline 0.5 gm were used in seven patients. Six of these reported good results, while in one the response was moderate.

CONCLUSIONS

1. The value of Orthoxine in bronchial asthma was studied in two controlled groups.
2. In both studies there was a decrease in symptoms while on Orthoxine compared to placebo. However, this difference was not statistically significant.
3. In an uncontrolled group of adult office patients 91 per cent reported definite benefit after the use of 100 mg tablets of Orthoxine.
4. The syrup of Orthoxine was also efficacious in children.
5. A combination of Orthoxine, aminophylline, and hyoscyamine hydrobromide gave good results in all of ten patients. However, the use of this particular combination is not suggested because of possible reactions to the hyoscyamine component.
6. A two-stage tablet of Orthoxine was also found to be effective, as was another mixture of Orthoxine, Pyrrolazote and aminophylline. Good results were also noted after the use of Orthoxine and aminophylline when given by suppository.
7. Side reactions were mild, transient, and infrequent.

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MYOCARDIAL CHANGES PRECIPITATED BY HYPERSENSITIVITY TO ACETYLSALICYLIC ACID

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Brooklyn, New York

ANGINA pectoris due to hypersensitivity to acetylsalicylic acid has been reported by Shookoff and Lieberman.[3] In the three patients which they observed, the attacks followed the ingestion of 5 to 10 grains of aspirin and were accompanied by tachycardia, a drop in blood pressure, and signs of collapse. In one of the cases electrocardiographic changes appeared during the seizure but they were transient. In none of these patients was there a temperature rise, an increase in the sedimentation rate, or any other evidence of heart muscle involvement. The authors stressed the presence of arteriosclerotic heart disease in each of the cases cited.

The following report is of interest because it differs in several notable aspects from the instances of acetylsalicylic acid hypersensitivity observed by Shookoff and Lieberman. A review of the literature fails to reveal a similar case.

CASE REPORT

The patient is a fifty-seven-year-old white Hebrew man with an allergic background and a history of arteriosclerotic heart disease.

Family History: His son has had asthma from childhood.

Past History: About a year previous he suffered a generalized eruption which an internist labeled as "allergic." Seven years ago the patient began to suffer attacks of pain in the precordial region, radiating to his left shoulder and arm, and precipitated by walking one and a half blocks. He was told by a cardiologist that he had arteriosclerotic heart disease with angina pectoris. Other past history is noncontributory.

Present Illness: On October 10, 1949, the patient received the last of three injections of 300,000 units of procaine penicillin in oil for submaxillary adenitis which did not respond to sulfadiazine. On October 16, he began to itch intensely around the neck and the back of his head. The following day he felt "bumps" behind his ears. On October 19, he was confined to bed and given 50 mg of Pyribenzamine every four hours because of a massive angioneurotic edema of the right thigh. The remainder of the body was affected by a generalized urticaria with large wheals. Several days after treatment with Pyribenzamine had begun, the brawny edema of the right thigh had subsided. He still complained, however, of a mild pruritus, and he still suffered from slight papular urticaria. On October 27 he developed a temperature of 101 degrees F. and a red throat, which may well have been a local manifestation of his reaction.

Although warned against taking aspirin, he swallowed two tablets. Ten minutes later a massive red welt appeared over the entire body and he collapsed. He felt weak and dizzy when he recovered and complained of a sense of oppression on his chest.

Approved for publication February 18, 1952.

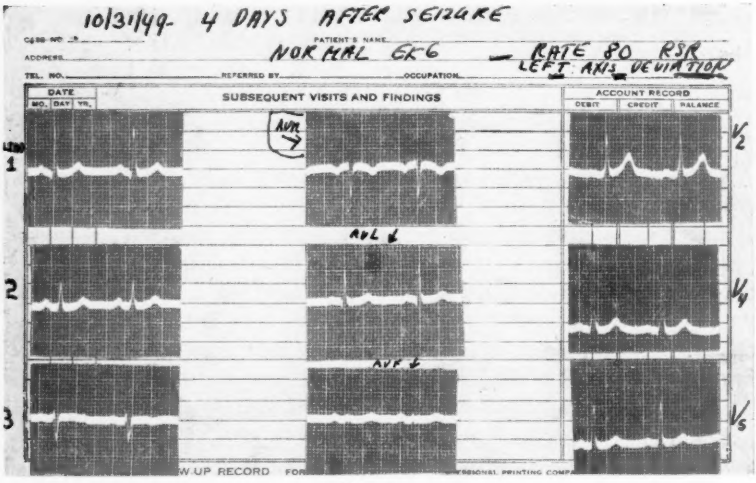

Fig. 1.

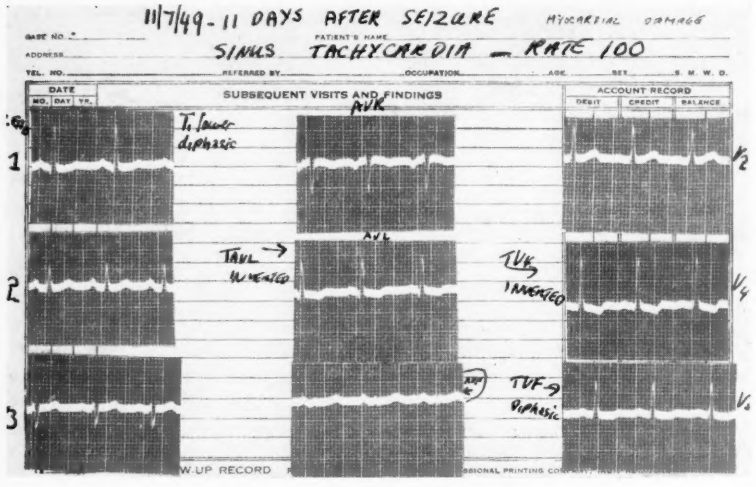

Fig. 2.

Physical Examination (one hour later): The patient was pale and apathetic. His heart sounds were distant, and no murmurs could be heard. The pulse rate was 98 beats per minute and the blood pressure was 90/70. (The systolic had previously never been lower than 120). The lungs were clear and there was no dyspnea. He had a generalized erythema, and giant wheals covered the entire body surface. The throat was injected. The rest of the examination was essentially negative.

Several minutes later the patient insisted on going to the toilet. Upon leaving, he collapsed for the second time within the hour after taking the aspirin tablets, and his face became an ashen grey. The pupils were dilated. Respirations were suppressed and his pulse was imperceptible. However, a few moments later his breath-

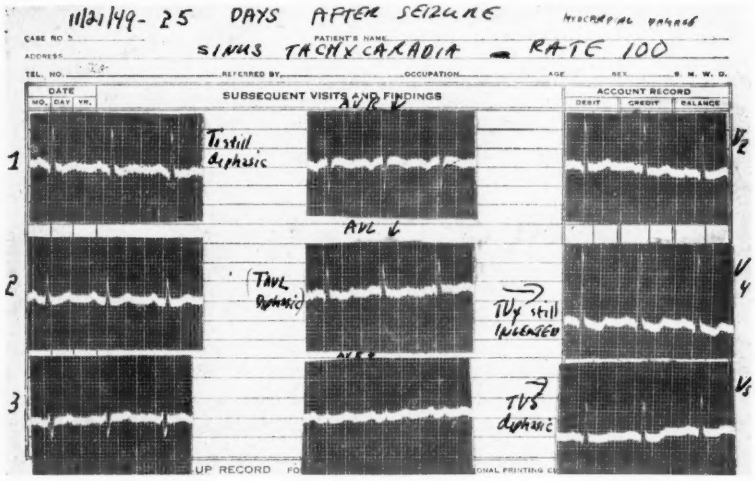

Fig. 3.

ing became deeper. The heart sounds were inaudible and the pulse rate was 130 beats per minute. The blood pressure fell further to 70/50. The lungs were clear and his respirations shallow and rapid. He complained of substernal pain.

Clinical Course: The following day the blood pressure was 90/70 and his pulse was 92 beats per minute. The heart sounds were barely audible. The rash receded and he had a rectal temperature of 100 degrees. He complained of a sense of oppression in his chest. Four days later, the blood pressure was 110/70 and the pulse about 80 beats per minute. The heart sounds were of somewhat better quality, and a soft systolic murmur was now heard at the apex. Although the fever and the rash were gone, he still complained of itching over the entire body. An electrocardiogram was entirely normal, but the sedimentation rate was 24 mm/hr (Cutler method). This was four days after his collapse. On November 7, or eleven days after his seizure, his blood pressure had risen to 115/70, and the sedimentation rate was 22 mm/hr. An electrocardiogram was repeated and showed evidence of anterolateral wall involvement. T1 was diphasic. Tavl was inverted. TV4 was deeply inverted and TV5 was diphasic. The heart rate was 100. On November 31 (twenty-five days following the attack) the blood pressure was 120/80 and the heart sounds were of fair quality. The electrocardiogram was identical with the one taken two weeks previous. It still showed evidence of myocardial damage. The patient made an uneventful recovery.

DISCUSSION

Clinically this patient had an attack of coronary thrombosis. This was evidenced by the rapid sedimentation rate, the fall in blood pressure, and the electrocardiographic changes showing myocardial damage which appeared eleven days following his seizure and persisted for fourteen days more. It appears likely that the attack of angioneurotic edema which preceded the cardiac complications was due to penicillin. In all probability a similar process may have taken place in the heart in an individual who

had an underlying sclerosis of the coronary vessels, which may have participated in the generalized penicillin reaction of the serum sickness type. The ingestion of the acetylsalicylic acid may have been an additional allergenic excitant which may have contributed to the reaction in the coronary vessels. That penicillin is capable of inciting reaction in the coronary vessels has been shown by Felder, Felder and Harkavy.[1] Felder and Felder[2] report a similar case of a fifty-nine-year-old white man who suffered a severe serum-like reaction due to penicillin. One of the manifestations of this condition was involvement of the myocardium with transient T wave changes. These changes are explained by the authors as being due either to edema of the myocardium or to diminished coronary blood flow.

SUMMARY

An attack of myocardial infarction precipitated in an allergic individual with arteriosclerotic heart disease followed a severe penicillin reaction. It is conceivable that besides the penicillin sensitization aspirin may have acted as an additional allergenic excitant, although there is no direct evidence. This was indicated by a new outbreak of severe generalized urticaria with giant wheals which came only ten minutes after ingestion of the aspirin tablets.

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2135 79th Street

ALLERGENS AND POLIOMYELITIS

The injection of extracts of house dust, pollens, or molds into mice does in no visible way influence the development of a simultaneous infection with the Lansing strain of poliomyelitis virus. This is in sharp contrast with the observations on Salmonella or pertussis vaccines and on diphtheria toxoids, which significantly shorten the incubation periods of similar infections. These experimental data, reported at the Boston meeting of the Society of American Bacteriologists (April 27 to May 1, 1952),* supplement in a significant way the results of a countrywide survey made by Dr. H. A. Abramson under the auspices of The American College of Allergists (reported at the A.C.A.'s Pittsburgh meeting), which showed no evidence of a deleterious influence of "allergenic" antigens upon human poliomyelitis.

*Bacteriol. Proceed., p. 102, 1952.

The Editor's Page

THE TREATMENT OF HAY FEVER

Never has the Latin tag *Obscurum per Obscurius* been better exemplified than by the present-day method of treating hay fever.

When, forty years ago, John Freeman began to use injections of pollen extract for the amelioration of pollenosis, his Clinic was open only one day weekly. For four decades since then, millions of patients have taken hundreds of millions of injections in accordance with a tradition attached to a method of treatment which, as far as we know, does not depend upon a seven-day physiological cycle.

In 1930, Freeman publicized his "rush method," frequently revised by other workers. Beginning with high dilutions of extract, the patient is given injections at two-hour intervals from 8 A.M. to 10 P.M. On each successive day an extract ten times stronger is used, for a total treatment period of five days. Similar courses are given if and when a relapse occurs.

In 1932, Bray first used the "shock method"; initiating treatment with the strongest solution available, he combined each dose with 25 per cent of its volume of epinephrine (1:1000). With a first dose of 0.08 cc, successive doses given at three- to four-day intervals were increased by 0.08 cc to a total of 0.24 cc, following which the interval between injections was widened to once weekly, for a top dose of 0.64 cc. Additional epinephrine was used as necessary, and ephedrine was given by mouth four-hourly during the course of treatment, the injection schedule being maintained despite the presence of local or general symptoms.

During the intervening years have been seen preseasonal and coseasonal injections, given either alone or combined into perennial treatment. Antihistaminic agents have taken the place of epinephrine and ephedrine for some types of "rush" treatment. The local reaction has been taken as an indicator for "shock" treatment. Some workers begin with small preseasonal doses based on skin test sensitivities, with no regard for previous immunity as evidenced by blood or ophthalmic or nasal tests. Others inject the dose the patient last took safely without reaction, arguing that it measures the patient's tolerance and is therefore safe, no matter how much time has elapsed. Injection into several sites simultaneously is used as a method of minimizing reactions, whereas in actuality the rapidity of absorption is thereby hastened.

Some allergists insist that the larger the dose, the greater the immunity. An attempt is made to take each patient to a predetermined level, using 2.0 to 3.0 cc of the most concentrated extract which can be prepared. Others level off at the dose they reach during the season in which no symptoms occurred.

To make confusion worse confounded, there are others who, for instance, use only one concentration of extract, say, 1:5000, and limit the amount injected from 0.1 to 0.3 cc. The immunological basis claimed for such injection therapy is that the patient is not thereby hypersensitized and that constitutional reactions are kept at a minimum, the injections acting anamnestically. If a patient lapses for two or three months, a booster injection of the same magnitude is given twice daily or every two or three days until remission is apparent.

Others go beyond this purely immunologic concept and use homeopathic doses. Excellent results are reported, especially in patients with seasonal symptoms and *negative* skin tests, with injections of minute quantities of dilutions as great or greater than 1 in one billion. By contrast, a homeopath must be considered as a coarse butcher.

Only brief mention can be given to the advocates of almost universal food allergy, who stress the complete elimination of all supposedly allergenic foods, a procedure which is said to permit the patient to do without injection therapy. Unfortunately, the amount of grape protein in brandy and of corn in the wax of the milk container is sufficient to precipitate symptoms, vitiating some of the results claimed.

And, of course, there are the "talk therapists" who either allow the patient to talk himself out of his hay fever or perhaps talk him out of it, explaining it away on the basis that conflict and anxiety cause nasal hyperfunction. This determines whether a given patient will or will not respond with coryza to pollen exposure. Why this should occur with only one pollen, and why sensitivity to it should be associated with production of reagin, is permitted to go unexplained, although comment is always made that, of course, injection treatment is really psychotherapy.

The permutations and combinations have by no means been exhausted. We have advocates of intracutaneous, subcutaneous, intramuscular, and (for the record) intravenous treatment. It has also been administered by iontophoresis. There are those who fervently stress the importance of a local reaction, and others of equally firm conviction that a local reaction is a sign of active hypersensitization.

The materials vary from whole pollen in suspension, with or without its oils, to extracts made with or without dialysis. Extracts are glycerinated, salted out, alum precipitated, acetonylated, heat precipitated, or chromatographically or electrophoretically "purified," and otherwise fussed up in any number of ways.

Some workers combine pollen extract with house dust extract, and others with a vaccine, stock or autogenous. Some physicians make mixtures of all the pollens to which a patient reacts by skin test, although no response to some such pollens can conceivably occur. Still others use ragweed pollen alone for fall symptoms, and timothy alone for all grass pollen-sensitive patients.

There are those who advocate the use of an omnium-gatherum of

all inhalants to which the patient reacts, including silk and orris root. There are those who add food extracts to such mixtures.

The methods of administration are just as varied. At the one extreme the patient is given a syringe, a dosage schedule, and a bottle of extract. At the other extreme, the physician not only gives the injection himself, but applies a tourniquet proximal to, or ice directly over the injection site, observing the patients at intervals during one or more hours.

The antihistaminic agents have been used around the clock, immediately preceding, accompanying, or following the injection.

Pollen extracts have been sprayed in the nose as part of a "hardening process." Phenol, zinc and silver salt solutions have been similarly used to fix the nasal mucosa. Pollen, in capsule form, has been given by mouth. There are no available reports of its use rectally, perhaps because the majority of patients would not willingly submit to insufflation or suppository techniques. Perhaps the authors were reticent concerning the negative results.

According to folk lore, painting the feet with iodine is good, but not as good as is rubbing the bark of an oak tree with a lock of the patient's hair cut during the dark of the moon. Slitting the throat from ear to ear or the use of "gravel, eight feet deep" is probably as efficacious as any remedies known.

There is no doubt that injections of pollen extract do something. But what is it they do? In some patients three injections give complete relief. In others, three years of treatment may be without result.

The basic papers dealing with the problem of pollinosis are so few that they can be mastered in an afternoon. The papers on methods of treatment number in the thousands, and exhibit every pitfall of clinical evaluation. Soon, somewhere, someone must correlate these apparently mutually contradictory hypotheses into a comprehensible system of therapy, so that irrespective of personalities, practices and pocketbooks, the treatment of hay fever will rest on a rational foundation. As Lowell said (of another matter) "It is a chaos indeed, but a chaos swarming with the germs of evolution."

For the moment, it appears from the literature that the best way to treat hay fever is to have a patient with a normal nose. He must be relatively free of anxiety and conflicts. His other inhalant and food sensitivities must be minimal. It helps if he lives in an air-conditioned home and works in an air-conditioned office. His hobbies should preferably keep him indoors. He should like injections and be willing to pay for them. His vacation should be taken during the peak of the pollen season, in any pollen-free area. He should not object to taking symptomatic medicine which must give him excellent relief with an absence of side reactions. Of greatest importance is a short season, with low pollen count, and rain every three days, especially on week ends.

American College of Allergists Convention Echoes

THE PATIENT: PERSON OR CASE?

The Presidential Address

HAROLD A. ABRAMSON, M.D.
New York, New York

While in service during the last war, I first heard of The American College of Allergists when a note from one of the founders, Dr. Fred Wittich, told me of its formation. In spite of the complexities of my life at that time, even the remote possibility of being active in the chosen area of my life work was stimulating and appeared to be of great importance. I accepted Dr. Wittich's invitation and have been glad to actively participate since that time in the scientific and educational program of the College. During this period of activity I eagerly sought information and the strength to be derived therefrom of many of my colleagues. Among the many rich personal and professional relationships I should like to mention all but have time for only a few. Dr. Hal Davison's quiet perception of what was important often coincided with and strengthened my attitudes in those early days, as well as now. Your incoming president, Dr. J. Warrick Thomas, contributed in the same way. The broad insight of Dr. Jonathan Forman, especially in educational matters and in public relations, cannot be underestimated. Very often a subtle, genial, integrating personality is needed, and there I found Dr. French Hansel's advice of inestimable benefit. The privilege of being Chairman of the Program Committee for two successive years was part of my assigned duties. These never could have been adequately fulfilled without the insight, clinically scientific knowledge, and administrative ability of Dr. Harry Rogers. A broad understanding of the problems of allergy far removed from home was made possible for me by Drs. Homer Prince, Ethan Allan Brown, Boen Swinny, and Katharine MacInnis. To this group should also be added Drs. Leon Unger, Orval Withers, and Merle Moore. Some controversy arose over holding our first Symposium on Psychodynamics. I shall never forget that Dr. George Rockwell told me, "We disagree with some of your views on psychodynamics, but I am all for having them tested by the College." This exemplifies his vigorous spirit and scientific insight. Scientific programs in allergy with Dr. Bret Ratner and psychosomatic programs with Drs. Hyman Miller, Dorothy Baruch, and John Mitchell were inevitably enriched. Knowledge of the history of allergy and the importance of maintaining the tradition of allergy were often imparted to me by Dr. Harry Bernton. In many ways, Drs. Stoesser and Kaufman aided in formulation of concepts as to what was important in the structure of the College. No less important was that advice of many others active in the scientific work of the College, especially the pioneer-

Presented as the Presidential Address, Eighth Annual Congress of The American College of Allergists, April 7-9, 1952, Hotel William Penn, Pittsburgh, Pennsylvania.
Dr. Abramson is Chief, Allergy Clinic, Mt. Sinai Hospital, New York, N. Y.

ing spirit of Dr. Jonez. To all of these colleagues I am indebted for their stimulating personal and professional comradeship.

But most important of all to me, for basic concepts of both scientific and organizational allergy, was my association and friendship with Dr. Murray Peshkin. It was through him, through his support and through his understanding of whatever goals were crystallizing for the betterment of allergy and for the future and strength of The American College of Allergists, that constructive efforts for the future were not without some success. His efforts in this direction are well known to all of you, and I am hoping that you will take advantage of his keen insight, scientific understanding, and personal qualities to help guide the future of the College in the years to come.

I have thus far painted a somewhat calm picture of the growth of the College in its scientific framework. However, the growth of any vigorous pioneering group is not without controversies. New concepts come in, old concepts must be discarded and modified, discordant interests must be dealt with as fairly as consistent with the natural growth of a scientific organization. As a result there are many points of view which must be analyzed, scrutinized, and integrated for the welfare of our organization.

"What is allergy?" was a question raised and discussed with spirit in Dr. Forman's letters during the past year.

On the basis of my work and friendships in The American College of Allergists and in other scientific organizations, I should like to take this opportunity to tell you what I believe the present and future attitude toward the science and the practice of allergy might be. We all agree, I think, with the idea that allergies are basically immunologic phenomena. However, this basic notion requires modification because of historical developments. It is quite true that historically the notion of altered reactivity developed and gave rise to the concept of hypersensitivity and the word *allergy*. However, in many of the clinical cases, such as allergy to drugs and allergy to bacteria and to viruses, the immunologic phenomena are not clear. These are often assumed. Indeed, too much emphasis is still laid upon the fact that in many difficult cases of obvious clinical allergy, negative skin tests are often found, thereby inferring absence of allergy. Certainly, we must not be placed in the untenable clinical position of treating skin tests. It is rather dangerous to hypothesize a classical antigen-antibody reaction, since many clinically allergic conditions cannot be directly correlated with this type of phenomenon. It might be better to state that in certain cases of allergy the patient has either in the skin or in the blood serum or in other shock tissue some indication of a new type of hypersensitivity not as yet definitely proven by the classical antigen-antibody reaction. I doubt if we, as physicians, should lean too heavily on an isolated laboratory or animal test. The study of allergy and especially the *treatment* of the allergic patient is, therefore, not a study exclusively of the antigen-antibody reaction. The study of allergy is the study of the allergic patient as a complete unit, as a whole person; and to define the magnificent, intriguing specialty of allergy as a study of antigen-antibody reactions *only* is misleading and unworthy of our specialty. Let us take up, in this connection, some other controversial points. Should the word *allergy* apply to conditions like rheumatoid arthritis, multiple sclerosis, tuberculosis, and similar and related illnesses? It is my feeling that there is much justification for including syndromes of this type in our specialty. For example, large sums of money have been given by foundations for testing the allergic theory of multiple sclerosis. You all know that by

injection of certain extracts of brain tissue, disseminated lesions of the nervous system can be produced in animals which simulate very closely the clinical condition of multiple sclerosis. Also, arthritis is certainly one of the symptoms of serum sickness as well as other drug allergies. Rheumatic fever is now considered a problem of hypersensitivity as well as the other collagen diseases. Are we to neglect our clinical duty to arthritic diseases because of a historical concept valuable in its time but which now would restrict our scientific horizons? It is our function as physicians not to be misled by an incomplete brilliant beacon by thinking exclusively in terms of antigen-antibody reactions; but we should be guided by our interests in all of those aspects of medicine in which not only altered sensitivity has been proven but in which altered sensitivity of any type is obviously a logical possibility.

Are we justified in studying food allergies by means of blood tests? My answer is yes. While I believe personally that blood counts and similar devices to discover the presence of food allergies more often are not generally acceptable as being statistically significant, I nevertheless feel that we, as allergists, must leave no stone unturned. It is our duty to explore every avenue of approach. The history of science proves to us that some of the most spectacular discoveries are often made in unexpected ways and in areas unpredictable on the basis of known experimental data. For this reason, we must proceed, testing our theories and scrutinizing the results in terms of the patient as a whole. The cold logic necessarily connected with the simple notion of allergy as an antigen-antibody reaction does not hold in explaining the clinical manifestations of the allergic patient or in completely guiding the management of the allergic patient.

The statement was explicitly made in a recent communication in Dr. Forman's letters that "spleen extracts, milk injections, typhoid vaccines, autohemotherapy, histamine, histaminase, histamine azoprotein, potassium salts, ethylene disulfonate are all confessions of failure." These are not failures but, rather, a manifestation of the inquisitive spirit of our colleagues in allergy. May I remark that hindsight is very safe and simple. It is inevitable in the history of medicine that new concepts must be tested in the face of possible failure. Is progress to be made by gloomy scientists who worship a chemical reaction which can't be shown to be present explicitly in most cases of allergy? I think the answer is no. I think that we must give free rein to our imaginations and weigh the results with temperate understanding and with scientific tolerance.

The most unjustified and harmful attack upon the subject of clinical allergy has been made by those who oppose treating the allergic patient as a complete person. This group of physicians apparently oppose treating as seriously as it deserves the emotions of the patient as part of the allergic syndrome. I think all of us who have seen the anxious, the depressed, or the grieving allergic asthmatic patient know full well that status asthmaticus or intractable asthma is not entirely dependent upon a simple antigen-antibody reaction. Most of us do know that the reassurance, the understanding, the sympathy of the doctor, not only in the field of allergy but in the entire field of medicine and surgery, is most important to the welfare of the patient. We as physicians must discover the balance of body-mind dysfunction in every patient. We must not only study and treat the skin reactivity but also any other reactivity of the patient including his emotional reactivity and its imbalance if this is found to be important. The practicing physician must therefore treat the patient not

only on the basis of the physical etiology of the illness but also on the basis of the patient's neuropsychiatric reaction to the illness. The patient's reaction to a chronic illness is invariably accompanied by anxiety. In other words, if we are to be what Murray Peshkin calls "compleat allergists," we must make it our duty to treat as far as possible (1) the manifestation of an imbalance in the antigen-antibody reaction, (2) any developmental basic anxiety of the patient, and (3) his anxiety toward his own illness and environment. This method of therapy is psychosomatic therapy.

One of the confusing elements is that some often use the term *psychosomatic* when *psychogenic* is meant. Psychosomatic allergy will always include a study of the soma and its antigen-antibody reactions. Those opposed to including the psychosomatic problem in the management of the allergic patient usually begin and end by attacking psychoanalysis. Indirectly, I have been the target for such attacks because I personally found it desirable at times to use psychoanalytic theory and practice. I should like to make it clear that I have never advocated psychoanalysis for all, or indeed for even a small number, of allergic patients or for doctors practicing allergy. It is true that I have recommended to certain of my colleagues, and few of these at that, that they would be helped in their personal and professional lives if they would be analyzed. Psychoanalysis for the physician who wishes to deal with the emotional problems of his patients in a more direct and in a more understanding way is just another valuable tool in the physician's hands. At present, I should say that psychoanalysis is indicated for less than 2 per cent of patients in allergic therapy. There are many reasons for this small fraction, which I could give you if time permitted under the heading "Indications." All physicians are psychotherapists. Psychotherapy of the allergic patient begins the first moment he steps into the doctor's office. The whole relationship of the patient and the doctor is always a psychosomatic relationship. Even if the doctor rejects the importance of the role of the emotions in the etiology of allergic disease, the relationship is still psychosomatic because the patient will feel that the doctor is emotionally uninterested in the patient's mental tensions. One of the most important developments in recent years of special interest to allergists, though not as yet a subject of study by them, is the fact that the nerve gases which have been described by Col. Wood in a recent article produce asthma in very small concentrations and in addition produce mental symptoms such as confusion. The syndrome of the nerve gas poisoning, therefore, is a psychosomatic syndrome with asthma. The control of this psychosomatic syndrome is of great import, and we allergists whose specialty centers about the study of asthma should recognize that this essentially military situation represents a classical psychosomatic syndrome which is basically connected with our own studies and responsibilities. Here is an important type of asthma, definitely not connected with the antigen-antibody reactions but closely connected with enzyme reactions and with the emotional patterns of the patient.

What does all of this mean for the future of allergy?

The standards connected with the antigen-antibody reactions and their evaluations in clinical allergy should be maintained and wherever possible raised, especially by the establishment of an active Board of Allergy for certification of allergists. I believe that our Instructional Courses should lay more emphasis on the management of the allergic patient as a psychosomatic entity and not only as an illness characterized by an antigen-antibody reaction. I believe that the subject of scientific and clinical allergy is growing and not contracting, as some misguided allergists have

ventured to say in recent publications and at recent meetings in connection with certification of allergists. I believe that allergy is growing in the direction of the coördination of the study of organ allergy and neuropsychiatric allergy with a great deal of emphasis on the emotional responses of the patient, especially toward his allergic illness. It is growing toward the point where we, as physicians, should be willing and ready to face our educational, scientific, therapeutic, and military responsibilities in dealing with the problems of allergy not only from the rigid point of view of a useful but narrow historical concept but also from the modern, more flexible concept that the clinical management (not the etiology) of the allergic diseases is a psychosomatic problem.

Finally, I wish to express my thanks to the present Board of Regents for their co-operation and to Mr. Eloi Bauers, our honored counsel, for guidance and support.

133 East 58th Street

PROCEEDINGS OF THE EIGHTH ANNUAL CONGRESS

The Eighth Annual Congress of The American College of Allergists was held at the Hotel William Penn, Pittsburgh, Pennsylvania, April 7, 8, and 9, 1952. It was combined with and preceded by a three-day intensive Graduate Instructional Course in Allergy (April 4, 5, and 6). The number of physicians registering for the Instructional Course was 177, for the Congress 560. There were six scientific exhibits, and forty-four technical exhibits of products relating to allergy and allied subjects.

The Program Committee, of which Dr. Giles Koelsche was over-all Chairman, and the Instructional Course Committee, with Dr. Hal Davison, Chairman, and Dr. James Mansmann, Co-Chairman, are to be congratulated on conducting one of the most successful conventions the College has ever had.

At the Instructional Course thirty-nine lectures were presented which covered every phase of allergy, commencing with the basic principles of allergy and immunology and ending with practical office and laboratory procedures. There were four round tables on Psychodynamics, Diagnosis and Treatment of Asthma, Industrial Allergy, and Allergic Skin Diseases in Infants, Children, and Adults, respectively.

On Friday, April 4, a luncheon lecture was held on "The Physiology of Respiration and Functional Tests" by Dr. Moses Campbell, Jr.; and Saturday was highlighted with a luncheon lecture on "The Integration of Allergy and Internal Medicine" by Dr. Lucien A. Gregg.

On Sunday there was a luncheon lecture on "The Management of the Allergic Child" by Dr. Stuart S. Stevenson.

The General Session opened Monday morning, presided over by Dr. J. Warrick Thomas, President-elect. There were fourteen lectures on this day.

On Tuesday morning Dr. Harold A. Abramson gave the presidential address, followed by the guest speaker, Dr. Alexander S. Weiner, Transfusionist to the Jewish and Adelphi Hospitals of Brooklyn, New York, as well as Senior Serologist to the Office of the Chief Medical Examiner of New York City. His subject was "The Solution of Certain Fundamental Immunologic Problems by Studies on Rh Sensitization."

CONVENTION ECHOES

On Tuesday there were two very well-attended round table luncheons, one on Psychosomatic Allergy and the other on Pediatric Allergy, and on Wednesday at 12:30 there were two more, one on Dermatologic Allergy and one on Otolaryngologic Allergy. Meantime, ladies and guests enjoyed the fine hospitality provided by the Pittsburgh Local Committee on Arrangements and the Hostess Committee. These committees functioned so outstandingly and successfully that it is only proper that they be listed at this time.

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Mrs. Alex R. McCormick

Assisted by Mrs. J. Warrick Thomas, *Honorary Chairman*

Entertainment for guests consisted of a conducted tour of the H. J. Heinz plant, the Mellon Institute of Industrial Research, a flower show, and through the courtesy of the Pennsylvania Allergy Association, Inc., a Ladies' Luncheon and Godey's Fashion Review, directed by Mrs. E. E. Kirkwood, Youngstown, Ohio, showing a trousseau about 150 years old.

BUSINESS MEETING

The following officers were elected, and, in due course, have assumed their respective offices and will serve until their successors are elected:

President—J. Warrick Thomas, M.D.
President-elect—M. Murray Peshkin, M.D.
First Vice President—Morris Kaplan, M.D.
Second Vice President—Henry D. Ogden, M.D.
Secretary-Treasurer—Fred W. Wittich, M.D.
Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.
Board of Regents—Three-Year Term
Harry S. Bernton, M.D., Washington, D. C.
Vincent Derbes, M.D., New Orleans, La.
L. E. Seyler, M.D., Dayton, Ohio

Therefore, the present Board of Regents consists of:

	Term Expires
Norman W. Clein, M.D., Seattle, Wash.	1953
L. O. Dutton, M.D., El Paso, Texas	1953
Stephan Epstein, M.D., Marshfield, Wis.	1953
Hyman Miller, M.D., Beverly Hills, Calif.	1954
Bret Ratner, M.D., New York, N. Y.	1954
Walker Rucks, M.D., Memphis, Tenn.	1954
Harry S. Bernton, M.D., Washington, D. C.	1955
Vincent Derbes, M.D., New Orleans, La.	1955
L. E. Seyler, M.D., Dayton, Ohio	1955

J. Warrick Thomas, M.D., as President, becomes the tenth member of the Board.

Dr. Wittich, Secretary-Treasurer, presented a complete financial report covering ANNALS OF ALLERGY for the year ended November 30, 1951.

Dr. George E. Rockwell, Chairman of the Finance Committee, presented a written report covering College finances for the year 1951, and this was supplemented by a complete certified audit report of the College.

The chairmen of the various committees, Dr. Ethan Allan Brown for the New and Unused Therapeutics Committee, Dr. James Stroh (by letter) for the Pollen Committee, and Dr. Murray Peshkin for the Certification Committee, all presented reports on behalf of their respective committees which were accepted and approved. Dr. Peshkin proposed the following resolutions which were voted upon and adopted:

1. WHEREAS The American College of Allergists has appointed a committee to co-operate with the committee of The American Academy of Allergy in matters pertaining to the establishment of an American Board of Allergy, and
   WHEREAS this committee has presented this plea for five consecutive years to the Committee on Standards and Examinations of the Advisory Board for Medical Specialties, and,

   WHEREAS this plea for an American Board of Allergy has been denied five times, and in view of the foregoing it appears desirable and urgent that the Fellows of The American College of Allergists reaffirm their support of the committee they appointed for a plea for an American Board of Allergy,

   BE IT HERE AND NOW RESOLVED that the Certification Committee representing the College be given a vote of confidence that it truly represents the desires of the voting Fellows of this College in its unselfish attempt to establish an American Board of Allergy.

   AND BE IT FURTHER RESOLVED that the Certification Committee heretofore mentioned be instructed to vigorously continue its attempt to establish an American Board of Allergy within the framework of organized medicine in any way it deems fit.

2. WHEREAS The American College of Allergists has resolved to support its Certification Committee for the establishment of an American Board of Allergy, BE IT HERE AND NOW RESOLVED that this Committee continue to co-operate with the similar Committee of The American Academy of Allergy in all activities pertaining to and leading to an American Board of Allergy.

An Honorary Fellowship was conferred upon Dr. Bernard Halpern of Paris, France, Secretary-General of the International Association of Allergology; Director of Research of National Center for Scientific Research of Paris; Chief of Laboratory, Faculty of Medicine, Paris, France; Laureate of the Academy of Sciences, Institute of France; Laureate of the Academy of Medicine of Paris; Secretary of the French Allergy Society.

The Secretary-Treasurer read the minutes of the previous meeting, which were approved and accepted. He also reported the membership up to date as 1056, although there are a large number of applications which have not been passed upon by the Board.

We report with sorrow that during the past year the College sustained through death the loss of the following members:

Dr. Allen Olson
Dr. Cecil W. Dingman
Prof. Dr. Robert Doerr
Dr. Clair A. Buck

Obituaries appeared in ANNALS OF ALLERGY, and condolences were sent to the families.

The Nominating Committee, consisting of Hyman Miller, M.D., Chairman, John D. Gillaspie, M.D., Bret Ratner, M.D., Lester L. Bartlett, M.D.,

Walker L. Rucks, M.D., and L. J. Halpin, M.D., after due deliberation and consideration, submitted the following slate on the official ballot to be voted on at the 1953 annual election as follows:

President-Elect—Homer Prince, M.D., Houston, Texas
First Vice President—Mayer Green, M.D., Pittsburgh, Pennsylvania
Second Vice President—Frank Simon, M.D., Louisville, Kentucky
Secretary-Treasurer—Fred W. Wittich, M.D., Minneapolis, Minnesota
Asst. Secretary-Treasurer—Albert V. Stoesser, Minneapolis, Minnesota

Board of Regents—Three-Year Term

Sam H. Sanders, M.D., Memphis, Tennessee
Boen Swinny, M.D. (served as Regent 1948-1949, 1949-50, 1950-51), San Antonio, Texas
Cecil Kohn, M.D., Kansas City, Missouri

The first half of the afternoon of Tuesday, April 8, was devoted to a Section on Psychosomatic Allergy, and the second half to a Section on Pediatric Allergy. At 6 P.M. there was a very well-attended and happy cocktail hour in the Fort Duquesne Room through the courtesy of Schering Corporation, Bloomfield, New Jersey. This was followed by an elaborate banquet at 7 o'clock in the Urban Room. Wine was furnished through the courtesy of Nepera Chemical Company, Yonkers, New York. There was a floor show of one and one-half hours followed by dancing. The floor show and orchestra were furnished through the courtesy of:

Allercreme Cosmetics ..... San Antonio, Texas
Baxter Laboratories ..... Morton Grove, Illinois
The Borden Company ..... New York, New York
Hollister-Stier Laboratories ..... Seattle, Washington
Luzier's, Inc. ..... Kansas City, Missouri
Marcelle Cosmetics, Inc. ..... Chicago, Illinois
Nepera Chemical Company ..... Yonkers, New York
Pennsylvania Allergy Association ..... Philadelphia, Pennsylvania
Chas. Pfizer & Company ..... Brooklyn, New York
Pittsburgh Allergy Society ..... Pittsburgh, Pennsylvania
Schering Corporation ..... Bloomfield, New Jersey
Smith, Klein & French Laboratories ..... Philadelphia, Pennsylvania

In this, the Local Committee on Arrangements exceeded the expectations of all by furnishing an orchestra and floor show composed of outstanding local and current vaudeville acts from the Pittsburgh theatres which appeared to be very well received.

Following the business meeting at 12:30 the round table luncheon on Psychosomatic Allergy was conducted by Harold A. Abramson, M.D., New York, moderator, and the topic was "Brief Psychotherapy in Allergy" with the audience participating. At the same time there was a round table luncheon on Pediatric Allergy, the moderator being Jerome Glaser, M.D., Rochester, New York, with a panel on "The Use of Meats as a Source of Protein in Milk Substitutes in Allergic Gastrointestinal Disturbances in Early Infancy," and papers on "The Significance of Nasal Eosinophilia" by Dr. Julia Baker of Mexico City, Mexico, and "The Optimum Dose of Pollen in the Treatment of Pollinosis" by Dr. Samuel J. Levin of Detroit, as well as a group discussion on "The Role of the General Practitioner and the Pediatrician in the Care of Allergic Children."

The Section on Psychosomatic Allergy met on Tuesday afternoon, with John H. Mitchell, M.D., Columbus, Ohio, as chairman. Papers were given on "Objective Psychological Tests in the Study of Bronchial Asthma," "Some Aspects of the Psychopathology of Asthma," "A Com-

parison of the Psychodynamics in an Exacerbation of Infantile Eczema with that of an Asthmatic Attack in the Same Individual," and "Self-inflicted, Food-induced Allergic Illness."

The second half of the afternoon was given to the Section on Pediatric Allergy, with Bret Ratner, M.D., New York, as chairman. Papers were presented on "Incidence and Progression of Allergic Syndromes in Children," "Soy Bean Milk as a Substitute for Other Milks during the Newborn Period," "Serum Levels of Potassium, Phosphorus, and Sodium during the Exudative Phase of Infantile Eczema," "Reactivity of the Skin of the Newborn," "Analysis of Protein Sensitivity in Childhood Eczema and Bronchial Asthma in Children."

Adolph Rostenberg, Jr., M.D., Chicago, was chairman of the Section on Dermatologic Allergy Wednesday morning, April 9. In this section papers were presented on "Papular Urticaria and Its Relationship to Insect Allergy," "Some Investigative Studies Concerning Reactions to Insect Bites," "Dermatitis Due to Inhalants," "Evidence that Psoriasis is an Allergic Disease," "Hypoallergic Penicillin IV (Chlor-Trimeton-Penicillin)," "Relief of Itching by Oil Soluble and Suspendable Epinephrine Compounds," "A Critique of the Evidence for the Allergic Basis of Collagen Diseases."

The second half of Wednesday morning was given to the Section on Otolaryngologic Allergy, with Walter E. Owen, M.D., Peoria, as chairman, and the following papers were read: "Otolaryngologic Examination of an Allergic Patient," "Allergy in Sinusitis," "Nasal Surgery upon the Allergic Patient," "Allergy of the Ear," "Allergic Headache," "The Use of Toxoid and Pathogenic Molds," "Seasonal Allergic Iritis."

At 12:30 there was a round table luncheon on Dermatologic Allergy, with Adolph B. Loveman, M.D., Louisville, Kentucky, as moderator. There was a panel discussion on "Neurogenic Factors in Contact Dermatitis," "Atopic Eczema in Infants and Children," and "Immunologic Factors in Contact Dermatitis."

There was also another round table luncheon at the same time on Otolaryngologic Allergy with George E. Shambaugh, Jr., M.D., Chicago, as moderator. The panel discussed "History of Dilute Dust Therapy," "Comparative Results of Concentrated Dust Therapy with Dilute Dust Therapy," and "Personal Experiences with Dilute Dust Therapy."

The afternoon session was given to a Section on Industrial Allergy, with Mayer A. Green, M.D., Pittsburgh, acting as chairman. Two papers were given, one on "Allergic Problems in Modern Industry" by guest speaker Raymond R. Suskind, M.D., Associate Professor, Department of Preventive Medicine and Industrial Health; Assistant Professor of Dermatology and Syphilology, College of Medicine, University of Cincinnati, Cincinnati, Ohio, and the other, "Detecting the Causes of Industrial Dermatitis by Means of Evaluating the Pattern" by George L. Waldbott, M.D., Detroit.

The membership and officers of the College are deeply grateful to those who made the scientific and technical exhibits such a success.

NEXT ANNUAL CONGRESS

The next Annual Congress of the College will be held at the Conrad Hilton, Chicago, the world's largest hotel, April 24-29, 1953. These dates do not interfere with any holidays. Arrangements are being made for an Instructional Course for the first three days, followed by the three days of Scientific Session. Dr. Giles A. Koelsche, Consultant Physician, Divi-

sion of Internal Medicine, Mayo Clinic, Rochester, Minnesota, was again elected over-all Chairman of the Program Committee, with Dr. J. Warrick Thomas, President, and Dr. Fred W. Wittich, Secretary-Treasurer, the other members of the Program Committee. Dr. Morris Kaplan, Chicago, Illinois, is Chairman of the Local Committee on Arrangements, and Dr. Leon Unger, Chicago, is Chairman of the Instructional Course.

Registration will begin on Sunday, April 26, 1953, at 2:00 p.m., and will not in any way interfere with the attendance at the Instructional Course. Following the custom already established, there will be no technical or scientific exhibits on Sunday. These will be featured on Monday, Tuesday, and Wednesday, April 27, 28, and 29. A scientific program will also be held on these three days. As formerly, there will be sections on Psychosomatic Allergy, Pediatrics, Dermatologic Allergy, and Otolaryngology, and probably others. There will be numerous luncheons and panel discussions.

Arrangements have been made to hold the 1954 meeting at the Chalfonte-Haddon Hall Hotel, Atlantic City, in either April or May.

COMMITTEE ON AEROBIOLOGY OF THE AMERICAN COLLEGE OF ALLERGISTS

The Pittsburgh meeting of the Board of Regents of The American College of Allergy, by formal action, established a permanent committee of the College to be known as the Aerobiology Committee.

At the present time this over-all committee shall be composed of five subcommittees as follows:

(1) The Mold Committee
(2) The Pollen Committee
(3) The Bacterial Committee
(4) Industrial Fumes and Dust Committee
(5) The Meteorological Committee

Each of these committees shall be composed of as many active working members as the chairmen of these individual committees recommend and shall be formulated during the course of this year. It is obvious, of course, that the scope of each committee is implied by its title and that it entails a tremendous amount of work and correlative effort. These individual chairmen have not yet been appointed by the Board of Regents, but will be in the very near future. It is hoped that the individual members of the College who are interested in taking part in any of these subcommittee activities will make themselves known.

Tentative plans are under way to have a joint seminar for discussion of this whole program with the committees and the effect of meteorology on health with the American Meteorological Society at the Chicago meeting. This latter group wishes to co-operate actively with the College when implementing this work.

Dr. L. O. Dutton, 616 Mills Bldg., El Paso, Texas, has been appointed by the Board of Regents as the over-all chairman of this highly important group. It is to be hoped that many members will respond by offering their services for the various activities of this group.

Progress in Allergy

ACTH AND ALLERGY

ETHAN ALLAN BROWN, M.D., F.A.C.A.
Boston, Massachusetts

In 1940, Armour & Company published a booklet entitled "The Pituitary Gland." Concerned with anatomy, physiology, cytology, and secretions, its sixty-eight pages represented a masterful synopsis of the basic information then available. Although the first work with adrenocorticotropic hormone had been started in 1938, it was not mentioned. Today, more than 5,000 references attest to the rapidity with which the laboratory and clinical properties of ACTH are being assembled. Those papers which are held for more than a few months before publication are out of date.

Since the reports, both confirmed and unconfirmed, appear in print almost faster than they can be assimilated, the subject in its present state is all but impossible to delimit. This is unfortunately equally true of other fields of science, in which, in all, approximately 175,000 papers are published each year, the annual rate of increase being 5 per cent. Of these, only about 10 per cent are abstracted. It would then appear that, for the moment, we cannot tell exactly where ACTH stands in relationship to the field of allergy. The present review does not pretend to be comprehensive. It assumes some knowledge of the subject, especially that which is available both in the manufacturer's brochures and in journals of easy access. Every aspect of the use of ACTH has certainly received more than its due share of publicity.

ACTH AND THE LUNGS

From the more than 100 papers dealing with the use of ACTH in the treatment of bronchial asthma and other pulmonary conditions, approximately forty-five will be reviewed. The criterion of choice is the contribution each makes to an over-all, fairly balanced point of view: one which, it is hoped, the reader can correlate with his own experience. A number of papers, repetitive or merely confirmatory of material long since proven to be valid, have been omitted.

One of the most recent communications on the subject, that by Arbesman[1] and his colleagues, is given precedence in that the papers which follow must be read in the light of its conclusions. In part, twenty-two patients with intractable bronchial asthma were treated by one or more courses of intravenous ACTH preceded by three to four days of injections of intravenous glucose and water. The total dosage necessary for a period of seven to nine days of treatment varied from 100 to 175 mg. Of the twenty-two patients eighteen were relieved of symptoms in forty-eight hours. The length of remission varied from fourteen to eighty-four days.

Dr. Brown is Physician-in-Chief, Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Massachusetts.

The expenses of the work described were defrayed, in part, by the Asthma Research Foundation, Inc., Boston 15, Massachusetts.

Five of the patients were given a second course of intravenous ACTH with successful remissions.

Arnoldsson and Pipkorn[2] treated four patients with bronchial asthma which had not responded to the usual types of therapy. ACTH (150 mg/day) by injection caused marked improvement noticeable within twenty-four hours and complete remission by the third day. The laboratory studies showed the usual reduction of blood eosinophilia in one patient. In two there was a leukopenia and in the other two, as well, a lymphopenia. The cholesterol values were markedly reduced. There was a rapid decrease in the glucose tolerance test with an increase in insulin sensitivity. The excretion of 17-ketosteroids was increased in one patient and only slightly increased in another. The paper is of interest in that the remission lasted for one week in one patient, for two months in two others, and for more than three months in the fourth, after a treatment period of only three days.

Barach's[3] report is concerned with sixty-eight patients suffering from bronchial asthma and the bronchospastic type of pulmonary emphysema. In all, 150 courses of treatment were given with complete cessation of asthmatic attacks following ninety and partial relief after forty. The average period of remission was seventeen days, excepting for six patients in whom it lasted for two to eight months. The most effective dose appeared to be 100 mg daily for four to five days with diminishing doses over a period of ten days. The patients were concomitantly placed upon a salt-restricted diet with potassium chloride (3 gm daily). In some patients, mercurial diuretics were necessary. Those patients in whom bronchial infection was proved to be present were treated in addition by other means, including antibiotic preparations. The original paper discusses in detail the side effects seen in ninety-seven of 200 asthmatic individuals in whom such associated bronchitis or bronchiectasis was present as treated by penicillin, chloromycetin or terramycin.

Blumenthal[4] reports on three patients who had not responded to ACTH. In a series of five patients studied by Bordley[5] and his associates all were benefited in periods of four to forty-eight hours with complete freedom from all asthmatic symptoms in one to eight days. The patients varied in age from twenty-six to sixty-three years, with asthma present for five to twenty-three years. The treatment periods varied from eleven to twenty-one days, with the initial intramuscular dose of 30 to 100 mg given q. 6. h. with a gradual decrease of the daily dose as the patient became symptom-free. The total amounts administered varied from 360 to 775 mg. In four patients the sputum and the abnormal physical chest signs totally disappeared. In one, although free of asthmatic symptoms, the rhonchi persisted. In three individuals an edematous, purulently discharging nasal mucous membrance subsided, and in two the nasal polyps completely or almost completely disappeared. In one patient the remission lasted one month. This paper reports that in one patient skin sensitivity to pollens and other extrinsic antigens diminished during the treatment period, to return to its original level in three weeks. In one other patient the skin tests were not affected.

In a second report one year later, Bordley[6] described the changes noted in the tissues of the upper respiratory tract following ACTH administration. The nasal mucosa is described as losing its swelling and acquiring a cover of thin clear mucus while developing a slate-pink color. Nasal polypi become less translucent, shrink, and in some cases disappear. Similar changes are noted in the nasopharyngeal lymphoid tissue. The author

concludes that both ACTH and cortisone have similar effects upon the membranes of the respiratory tract.

In a third report Bordley,[7] continuing his studies on the tissue changes seen in the upper respiratory tract during ACTH therapy, reports on more than sixty patients suffering not only from respiratory tract allergy but also from rheumatoid arthritis, lupus erythematosus, inflammatory eye disease, periarteritis nodosa, penicillin reactions, chronic hepatitis, myasthenia gravis, Ménière's syndrome, and oral pemphigus. In all of these, the mucous membranes became bluish pink; the mucopurulent discharge decreased; atrophic areas, crusts and ulcers cleared or improved; and the appearance of the nasopharyngeal lymphoid tissue became more normal. In fifteen of the patients who presented polyps or polyphoid changes with or without allergic bronchial asthma, there was a color change and diminution within twenty-four to seventy-two hours, and a decrease or disappearance of the polyps after two weeks. The allergic symptoms which had disappeared during the treatment period returned following cessation of therapy in two to twelve weeks, with reappearance of the polyps, excepting in two patients. It is interesting to note that the remission periods were abbreviated by the occurrence of respiratory infections. Eleven of the patients with a previous history of sinusitis had some evidence of recurrence successfully controlled by antibiotic treatment.

Brown[8] and his co-workers studied forty patients given ACTH (16 mg q. 6 h.) as the average daily dose. In the greater majority, the symptoms disappeared by the second or third day. The treatment was continued with smaller doses at intervals of twelve hours. In all, without exception, a relapse occurred when ACTH therapy was discontinued. The shortest remission was forty-eight hours and the longest ten days. Excepting in those patients in whom a known causative allergen was removed from the environment, or hypersensitization injections given, re-exposure caused an immediate exacerbation.

Burrage[9] reviewed the earlier reports on the use of ACTH in allergic disease. All of us must agree with his temperate conclusions, when he states that the more recent reports tend to refute the earlier more optimistic opinions that the problem of allergic disease is near solution. Burrage concludes that "while a strong impetus has been given to clinical research in allergy the fact still remains that the fundamental process by which ACTH and cortisone affect these allergic diseases is unknown and unmeasured in the terms of the known metabolic functions of the adrenal cortex. The complications following their use may be dangerous."

Carey et al[10] treated, in all, nineteen patients suffering from chronic intractable bronchial asthma. The daily doses of ACTH varied from 20 to 140 mg. The totals administered varied from 190 to 1248 mg, the treatment periods lasting from four to twenty-one days. In fifteen patients, there was a complete subjective and objective relief lasting from three to 263 days. In four patients, there was a 50 per cent or more decrease in the severity of the condition. Seven patients who had responded to a first course of ACTH therapy with complete remission relapsed. A second or third course given from six to 224 days later gave as complete and prompt a remission as did the first injections. Since seven of the patients had received placebo medication, their subsequent courses proved that their improvement was due to the ACTH and not to either environmental or psychogenic factors. The authors report that many of the skin reactions to the inhalants and bacterial antigens are significantly reduced during ACTH treatment. The side reactions noted include weight gain, edema,

increased fasting blood sugar levels, acne (six patients), hypokalemia (one patient), and hypertension (five patients).

Cook's group[11] reported on their studies of thirty-one patients presenting persistent severe bronchial asthma of bacterial or combined bacterial inhalant origin. The dose of ACTH was 80 mg daily in divided amounts at six-hour intervals, with a proportionally lower dose given to children. In this series of patients who were evidently severely ill, recovery took from ten to fourteen days, with the asthma returning within a few days or weeks following cessation of treatment. The laboratory studies done on the serum of nineteen adult patients with chronic infective asthma showed distinctly abnormal distribution of the protein fractions, the albumin and the alpha, beta, and gamma globulins. These were considered as caused by the underlying allergic state, and not due to the treatment with ACTH. It is concluded from their immunologic studies that the symptomatic relief and tissue alterations seen following ACTH therapy are not due to interference with the immediate wheal type of reaction of the antigen-antibody sensitized cells.

In a report concerned with fifteen patients varying in age from three to seventy years, Feinberg, Dannenberg, and Malkiel[12] describe the clinical courses of six who obtained complete remission lasting from ten to 165 days, with four obtaining moderate freedom from symptoms with either ACTH or cortisone. The patients received one or two courses of ACTH with the total dose varying from 235 to 1180 mg over a period of six to fifteen days. In these patients, however, quantitative studies of the ophthalmic and nasal reactions in those who had nasal or conjunctival allergy showed these not to be altered. Sensitizing antibodies remained unaffected by treatment with either corticotropin or cortisone. The authors conclude that the drugs are most helpful in intractable asthma, in acute status asthmaticus, and in severe drug reactions. Their usefulness is limited, however, by the fact that the length of remission after a single course of treatment varies from a few days to a few months, that some types of allergy do not respond, and that some conditions require frequent injections. They state, in addition, that it is, of course, possible that the simple titration tests used do not simulate the conditions of chronic allergy, and if there were tests devised to resemble more closely the continuous allergic stimulation that these patients suffer, the hormone injections might have been proved to have had a decisive influence on allergic reactivity.

In this regard Franklin, Lowell, Schiller, and Beale[13] recently reported on the twenty-five patients studied from December, 1949, to January, 1951. The average dose of ACTH given was 80 mg daily. There was complete relief in seventeen, marked relief in six more who required some medicine, and little or no effect in two who were bedridden for other disorders. Those not affected by ACTH were given cortisone with good relief. In two of the patients relapses occurred in twenty-four hours; in about half, remission lasted seven days; and in only seven was the period of freedom from symptoms more than seventeen days long, two such remissions occurring in the same patient following separate courses of treatment. The side effects seen include a paranoid psychosis; convulsions probably due to fluid retention; and in some patients, mooning.

The Friedlaenders[14] recently reported in this journal that they had studied ninety-one allergic patients, forty-one of whom presented a history of bronchial asthma varying in duration from two to thirty years, hospitalization being necessary in twenty-one. Ten were given an initial course of corticotropin by intramuscular injection in total doses of 600

to 870 mg over a period of eight to thirteen days. Good results were seen in six, with fair results in two and poor results in two more. The conclusion is drawn that remissions in bronchial asthma due to corticotropin and also cortisone are generally of brief duration, the symptoms recurring with their original severity within a few days or weeks, although repeated courses are frequently as quick in their results as the initial course. The relapses, however, in this group tended to recur more quickly and severely after each successive course of treatment. The side effects noted include fluid retention with edema, acne, menstrual dysfunction, psychic disturbances, and signs of adrenal insufficiency. The authors suggest, as do many workers in this field, that the drugs may be used to advantage as adjuncts in the temporary alleviation of the more severe symptoms associated with hypersensitivity. The advisability of using hormone treatment for long periods of time is questioned.

Galdston and his colleagues[15] described the results of ACTH treatment in five patients with chronic lung disease, of whom two suffered from asthma, one from senile emphysema, one from emphysema with bronchiectasis and healed tuberculosis, and one from Boeck's sarcoidosis. The dose varied from 40 to 80 mg daily, with a preceding control period during which water was substituted for ACTH, the respiratory functions being studied before and after the course of treatment. A patient with seasonal asthma of twenty years' duration with a disability of two years showed an unequivocal improvement in all of the measured pulmonary functions, the vital capacity becoming normal, the ratio of residual air to total capacity decreasing, and the maximum breathing capacity doubling. An exacerbation occurred, however, two weeks after ACTH treatment stopped. The second patient, who presented a marked thoracic deformity and cor pulmonale with nonseasonal asthma, showed no improvement during the treatment period. There was no improvement also in the patient with senile emphysema. Since emphysema was prominent in the first two patients, it is inferred that response to ACTH cannot be predicted from the pattern of the pulmonary-function defects present. No improvement was seen in the patient with bronchiectasis, emphysema, and bilateral apical tuberculosis, but in the patient with Boeck's sarcoidosis there was defervescence, regression of joint swellings and skin lesions, and improvement of respiratory function. There was no change, however, in the hilar lymph node enlargement. The respiratory improvement may have been caused by resolution of such sarcoid infiltrations of the pulmonary parenchyma as were not radiologically visible. Within two days after cessation of ACTH treatment, the fever, joint pains, and pulmonary signs and symptoms reappeared. It should be noted that in this series one patient developed mental depression and committed suicide when the treatment was discontinued. Since the two patients with pulmonary emphysema actually became, if anything, worse during the administration of 10 to 20 mg daily, the fluid retention may have diminished their cardiac reserve. It is concluded that ACTH apparently suppresses rather than cures the manifestations of disease.

In France, Harvier and his colleagues[16] reported on the effects of ACTH in twelve patients in status asthmaticus. The dyspnea ceased in twenty-four to thirty-six hours, with notable diminution of bronchial obstruction and expectoration. The remission period lasted for seven days in one patient, from three to six weeks in five patients, for three months in two patients, and for more than four months in three others. Only one patient did not respond. In three of the subjects studied, an associated eczema

disappeared in twenty-four to thirty-six hours. Excepting a slight transient glycosuria on two occasions, there were no untoward effects. Weight increase was noted and suggested as being due to water retention.

Herschfus, Levinson, and Segal[17] used their protection studies in order to discover the manner of action of ACTH in asthmatic patients. Thev had previously shown that a reproducible decrease in vital capacity (usually associated with dyspnea and wheezing and occasionally with cough) could be induced in sensitive asthmatic patients by the intravenous administration of histamine or methacholine. Their previous studies showed that the administration of six inhalations of an aerosol produced by a 0.5 per cent solution of Isopropylarterenol would immediately protect sensitive asthmatic individuals against the bronchospastic effects of histamine to a degree of 70 per cent, the significant protection persisting for about twenty-two minutes. The minimum significant level of protection is a value of 40 per cent. A single dose of ACTH, although it may produce a fall of circulating eosinophil cells greater than 50 per cent, confers no such protection. Their studies prove that ACTH is neither an antihistaminic nor an anticholinergic agent in the usual sense of the word. A single dose of ACTH has no beneficial effect upon acute paroxysms of bronchial asthma. Interestingly enough, a patient in status asthmaticus who experienced a fall in vital capacity of 1000 cc after the intravenous administration of 0.025 mg histamine, before ACTH treatment had a similar drop of only 400 cc after one day of ACTH therapy. After seven days of such treatment the decrease in vital capacity was only 200 cc. In another patient in whom the vital capacity decreased by 1400 cc following the intravenous administration of 0.01 mg of histamine, there was no alteration in vital capacity after the same injection when the patient had taken ACTH (410 mg) over a ten-day period. This and other studies show that the abnormal sensitivity of asthmatic patients to injected histamine may be lessened or abolished by treatment of ACTH, although the beneficial action of ACTH upon the course of bronchial asthma is not due to direct antagonism to either histamine or acetylcholine.

Holley[18] reported, on the other hand, that although his patients with chronic intractable bronchial asthma and status asthmaticus showed astounding improvement, in some cases, the symptoms returned while the patient was being maintained on the same dose. He feels that although short-term therapy may be life-saving, long-term therapy is not warranted because of the expense and possible untoward effects.

The series of nineteen patients studied by Howard et al[19] were given a total dosage of 193 to 1248 mg, the dose being gradually reduced to 20 mg/daily. In fifteen patients there was a complete remission of symptoms, with two of the remaining four presenting a partial remission. The symptom-free periods lasted from two to 263 days. Six of the nineteen patients who received subsequent courses of treatment all responded equally well.

North of the border, Kanee[20] administered ACTH (10 mg q. 6 h.) for two days and then q. 8 h. thereafter to an infant whose asthma had been present since the age of twelve weeks, requiring hospitalization for a period of seven months. Within twenty-four hours a concomitant atopic eczema showed marked improvement, with a general change for the better occurring by the fourth day. In ten days, however, there was an exacerbation of the eczema accompanied by stertorous and wheezy breathing followed by a rise in temperature and a troublesome cough. These additional symptoms

were considered as evidence of excessive fluid retention and electrolyte disturbance, although the serum potassium, sodium, and plasma chlorides were not found to be grossly abnormal. Further studies revealed the presence of pneumococci, Type III, hemolytic staphylococci and streptococci. The patient was given aureomycin, but several days later presented a typical clinical picture of varicella. The ACTH, which had been stopped, was once more started, with relief (not as complete as with the first course) occurring within four days. It was noted that within ten minutes after each injection of ACTH the patient became pale and listless. His color and tone did not return to normal for at least thirty minutes. Following each injection, also, there was a transient abdominal distention due, it was thought, to an oxytoxic effect of the ACTH. The eczema has recurred to a mild degree, but the patient's breathing has remained normal, excepting when he is emotionally upset.

When the side effects are partially respiratory in nature, they may complicate the clinical picture, as shown by the work of Keeton.[21] He and his co-workers describe two patients in whom dramatic respiratory symptoms were induced by the sudden withdrawal of ACTH treatment. The first patient, a forty-eight-year-old male, presented a progressively severe pulmonary fibrosis of unknown etiology of four years' duration, with a cor pulmonale and mild decompensation of six months' duration. His dyspnea, coughing spells, and nasal congestion all cleared with ACTH (20 mg q. 8 h.), but an exacerbation occurred in six hours after ceasing the treatment which had been given for a period of two months. His condition deteriorated so rapidly that hormone treatment had to be initiated at the earliest opportunity. This was followed by rapid improvement.

In order to study the mechanism of this reaction, the patient was hospitalized one month later. Following twelve days of ACTH treatment he was given forty-eight hours of placebo medication, and the same dramatic respiratory symptoms recurred. With gradual decrease in ACTH dosage, the patient was able to continue without incident. The authors conclude that withdrawal of the drug in patients with pulmonary disease should be carried out with great caution. In this regard, they quote Thorn, who at the First Conference on the Adrenal Cortex of the Josiah Macy, Jr., Foundation, said, "You treat for two weeks with 100 mg of cortisone. You then stop treatment. For two to five days you will fail to get an adequate adrenal cortical response to the ACTH test. In other words the adrenal has atrophied and it won't be brought back very easily by the ACTH during that period. I don't know just how long the period lasts. We have had cases that we are trying to follow. You can see after you stop the cortisone treatment that you are going to have the widest possible swing, because within two to three days you are going to go from essentially a Cushing's down almost into an Addison's range of adrenal secretion. You must hope that nothing happens to the patient during the week after you stop your cortisone therapy."

Although Thorn is referring to cortisone rather than to adrenocorticotropic hormone, one might reason with the authors that although the pulmonary tissue is particularly vulnerable to sudden deficiencies of glucocorticoids, on the other hand, defenses against infections are profoundly modified during and after the administration of pituitary adrenocorticotropic hormone.

The second patient studied by these authors was a fifty-year-old man suffering from chronic bronchitis and secondary emphysema of ten years' duration. ACTH (40 to 60 mg) over a forty-five-day period while the

patient was hospitalized and at home brought on slight improvement. However, seventy-two hours after the withdrawal of ACTH he became weak and dyspneic, requiring continuous oxygen administration. The ACTH was resumed without the patient's knowledge, and within twenty-four hours his clinical condition noticeably improved. It would appear from the studies done that in some patients tapering off is an essential part of ACTH treatment.

Krupp et al[22] used both ACTH and cortisone in private clinical work, reporting that alternate courses of both drugs proved successful in the treatment of a patient with chronic pulmonary berylliosis. In two patients with acute bronchial asthma ACTH (100 mg daily) resulted in a favorable response. Intravenous injections of only 10 to 25 mg daily helped three other patients with acute asthma. Because all of the patients were carefully selected and studied before treatment, the untoward effects observed were few.

At the Mayo Clinic Koelsche and a group of others including Maytum, Prickman, Carryer, and Peters[23] studied fifty-five patients varying in age from nineteen to sixty-nine years, all suffering from allergic disorders. Of twenty-seven with severe known seasonal bronchial asthma, thirteen, who received 140 to 2825 mg ACTH for three to 180 days, improved in periods of time from six to seventy-two hours. With one exception, the period of remission lasted from three to five weeks after cessation of therapy. In these patients there were no toxic reactions. No lessening of skin-test sensitivity was noted. In the same group were seven patients with hay fever who were moderately to markedly relieved during the course of treatment and for a few days afterwards. Five other patients suffering from vasomotor coryza had marked post-treatment relief lasting from a few days to a few weeks.

The effects of prolonged ACTH treatment of bronchial asthma were reported upon by Lowell, Schiller, Franklin, and Leard,[24] whose thirteen patients received either ACTH or cortisone for approximately one-third of the time between December, 1949, and September, 1951. In two patients the treatment was labeled "life-saving." Seven others who had had continuous asthma were termed "pulmonary cripples." The treatment brought marked relief in most patients with a dose of 80 mg or less daily. Although not completely relieved, the patients tolerated their residual mild asthmatic symptoms well and appeared to be satisfactorily treated with a smaller dose than that required to relieve bronchospasm completely. The authors feel that a middle course is the more desirable because of the possible deleterious effects of high dosage. The patients showed an increase in appetite, a gain in weight, and a feeling of increased energy. Laboratory studies show that prolonged treatment is not associated with any amelioration or progression of existing pulmonary pathological lesions. Side effects, however, including mooning, occurred in five patients, a diabetic type of glucose tolerance in three more and convulsive seizures in one. It would seem desirable from the point of view of this study to continue patients on sufficient ACTH treatment so as to control major symptoms, the minor asthmatic seizures being treated by other means.

Other studies on the effect of ACTH on pulmonary function were done by Lukas,[25] whose series comprises nine patients with various types of chronic lung disease. He concludes from the fact that subjective and objective improvement, sometimes dramatic, occurs in those patients whose disease is secondary to or complicated by bronchiolar obstruction but minimal or absent in those without obstruction, that ACTH exerts a sus-

tained bronchodilating action. The effect of ACTH on the bronchial tree was greater than the action of conventional bronchodilating agents in at least two patients with chronic obstructive emphysema. The studies were helpful in revealing the true extent to which the functional impairment could be attributed to a bronchiolar obstruction rather than to permanent anatomic changes. A depression of gas exchange seen in a patient with cor pulmonale was thought to reflect the development of edema of the alveolar membrane. Side effects of this type, it is concluded, are hazards of ACTH administration in patients with far-advanced chronic lung disease.

Massell, Warren, Stillman, and Bayles[26] treated, in all, 613 patients. They report that those with bronchial asthma were restored to normal in twelve to sixteen hours. The hay fever patients were given eight injections of 25 mg q. 6 h. for forty-eight hours and were completely relieved for the remainder of the season. The side effects listed include mental symptoms as manic, depressive or paranoid, congestive heart failure due to water retention in patients with weak hearts, and Cushing's syndrome. All of these, it is believed, might have been due to improper dosage.

McCombs and his colleagues[27] studied a series of twenty-three asthmatic patients, about half of whom also suffered from seasonal perennial coryza. Three were severely emphysematous. One presented a concomitant active eczema. The dose level varied from 10 to 40 mg (q. 4 h. to q. 8 h.) subcutaneously. Edema was controlled by a low-salt diet and mercurial diuretics. The side effects included some mooning and, in one patient, hives and nodules at the site of injections. Those responded to Pyribenzamine. In nine allergic patients the skin tests were not altered. The remissions lasted for a few days to some months and in one patient for four and a half months.

Paulsen's studies[28] are concerned with 112 patients in whom he was able to differentiate between pharmacological and clinical results. The physiological response was produced in normal as well as in sick subjects and was characterized by a fall of eosinophilic cells four hours after the injection of more than 4 to 5 mg ACTH. He reports that neither physiological nor therapeutical response was obtained in Addison's disease and in bronchial asthma associated with eosinophilia. A physiologic but not a therapeutic response was seen in a number of conditions, including pulmonary tuberculosis and chronic multiple sclerosis.

The effects of delayed action with ACTH are reported on by Peterman[29] who administered 20 to 100 mg daily of ACTH in 5 cc of a menstruum consisting of nonantigenic gelatin (18 per cent) and dextrose (8 per cent). Each patient was given fourteen to thirty-seven treatments over a period of seventeen to forty-three days. Although a single dose of 100 mg reduced the circulating eosinophilia from 1400 to almost zero within twelve hours, the count increased slowly over the period of the next forty-eight hours. Each succeeding daily injection was given before the effects of the preceding dose had worn off. Interestingly enough, when the eosinophil count was initially low, that is, approximately fifty cells, 40 mg ACTH produced an increase in eosinophilia for the first few days, with a peak count of approximately 350 cells in two days, and a subsequent decrease, usually to zero by the second week of treatment. The doses required using the menstruum were approximately 60 per cent less than those required with the conventional vehicle. Some patients complained of transient

local muscle soreness, and in two instances there was a general reaction consisting of mild chills, fever, and perspiration.

In another report issued by the Mayo Clinic, Prickman and his group[30] delineated the use of corticotropin in asthmatic patients being prepared for surgical procedures, notably in four patients in whom cholecystectomy, herniorrhaphy, and thyroidectomy had to be delayed. ACTH (5 to 20 mg) intramuscularly resulted in freedom from symptoms in four to eighteen days. In order to make certain that the doses given would not interfere with wound healing, the operations were delayed for an additional three to seven days. One patient developed a fluctuating abscess at the site of an intramuscular injection of ACTH, probably due to technique rather than to effects of ACTH. It subsided on incision and drainage. In all of these patients, asthmatic symptoms had developed from one to four years before surgery was necessary. Routine treatment had been ineffective.

Ten of eleven patients with bronchial asthma refractory to management by specific allergic diagnosis and therapy achieved marked relief for a remission period of one to twenty weeks following a single course of 125 to 325 mg of ACTH q. 6 h. as administered by Randolph and Rollins.[31] The relief noted varied from 50 to 100 per cent. Patients with food sensitivity were able to tolerate ingestion of allergenic foods without symptoms. Doses of house dust and ragweed pollen which previously induced constitutional reactions failed to do so during or immediately after the treatment period. In one patient, on two separate occasions, fluid retention followed ACTH therapy. ACTH was discovered to be least effective in patients with pulmonary emphysema and extensive scarring from pleurisy and emphysema.

What are probably the most complete studies of this field have been done by Rose and his associates, whose original papers merit detailed study.

In one report[32] six patients with severe intractable asthma who had been kept on a diet of known caloric and electrolyte values for sixteen days were given intramuscular injections of sterile water every six hours for a three-day control period. On the tenth hospital day ACTH was administered. The dosage schedule for two patients was 150 mg daily for two days and 100 mg daily for two more days. In four patients the dose was 100 mg daily for three days, 75 mg daily for two days, and 25 mg on the sixth day. In two patients there was marked improvement, and in four complete remission. The longest of such remissions was one month, with the asthma reaching its previous degree of severity within two weeks. In one patient a daily sputum output decreased from 800 cc to less than 200 cc by the fourth injection day. In all the other patients cough and expectoration disappeared. In all, the vital capacity and the maximum breathing capacity improved. There was only slight reduction, however, of polypoid formation and of thickened or hyperemic mucous membranes. Protection studies showed that ACTH prevented depression of respiratory function by histamine or methacholine injections. In most patients urine histamine completely disappeared. In all, urine histidine increased. In five patients the eosinophils were reduced to almost zero within twenty-four hours and by the sixtieth hour in the sixth. In two asthmatic patients, one with rheumatoid arthritis and the other with periarteritis nodosa, a complete remission of the bronchospasm occurred.

In a later report, Rose and his colleagues[33] published the results of their studies on fifty-three asthmatic patients treated with ACTH and cortisone. In forty-seven there was marked but temporary improvement,

the remissions lasting from two days to nine months after treatment periods of two to twelve days for those extrinsically sensitive. In those labeled as intrinsic, treatment periods of two to six days gave relief lasting three to five weeks. Of twenty-five severely ill bronchial asthmatic patients given ACTH and oral or intramuscular cortisone, seventeen were completely relieved, six partially, and two indeterminately. Of these, however, 50 per cent relapsed in one week after the cessation of therapy, and all but one subsequently relapsed. There were no serious reactions excepting a paranoid psychosis following ACTH treatment in one patient.

Rosenberg, who worked with ACTH of Astwood's preparation,[34] had the advantage of a fraction which was twenty times as active as the standard. The dose of Fraction C approximates 3 mg/day as compared with 45 mg/day of the usual material namely Fraction A. Both preparations are most effective when given every eight hours, and one or the other was given in all for a period of two to forty-three days to 211 patients presenting 230 multiple diagnoses. Of these, forty-three courses were given to twenty-nine patients with bronchial asthma, with marked relief in thirty-eight, moderate in four, and no improvement in one. The original paper gives the side effects in detail but notes that they were never serious.

Rowe et al[35] studied the effect of ACTH on epinephrine- and aminophylline-fast patients with bronchial asthma, seasonal pollinosis, and a number of other allergic conditions to be discussed below. They report a favorable response to both ACTH and cortisone, but a poor response in two patients with vasomotor rhinitis.

Corroborative results have been published by Salen,[36] who treated an aspirin-sensitive asthmatic female patient and saw her become symptom-free with only two days of ACTH administration. She remained free on doses as low as 5 mg daily. Cortisone (50 mg) daily was used as continuation treatment. Maintenance doses of 25 mg every other day kept the patient symptom-free for a two-month observation period. In five other patients with asthma, Salén used corticotropin followed by cortisone and, in all, epinephrine could be dispensed with and other drugs reduced to a minimum. There were no ill effects.

In his discussion of the effects of ACTH in six patients studied from thirty-two to forty-eight days, Samter[37] goes beyond reporting the good results of the Searle preparation in four and the moderate effects in two, discussing, in addition, the possible means by which ACTH mediates its effects. Before the days it was available for treatment, attention had been focused on two potential pathways through which the principal physiological mechanisms were thought to enter into the etiology of allergic manifestations: first, the liberation of histamine, the result of antigen-antibody reactions of the anaphylactic type; and, second, the "imbalance" of the autonomic nervous system with parasympathetic stimuli predominating. In support of the second hypothesis there are the studies which show that the patient with chronic bronchial asthma exhibits severe degenerative changes in the sympathetic chain. Other studies show that in the blood of asthmatic patients there are normal levels of cholinesterase activity and high levels of acetylcholine. To these Samter says we must add a third concept: namely, that of an ubiquitous shock tissue, the mesenchyme in which the ground substance, a mucopolysaccharide, exists under normal conditions as in an inert polymerised form. Injury or hormonal stimulation may cause enzymatic depolymerization, altering its structure and rendering it water soluble, changing its consistency and resulting in

the production of an increased number of reactive groups. The relatively inert glycoprotein is thereby converted into substances which may react with some of the diffusing constituents seen as the result of the altered permeability of the blood vessels. These three mechanisms may be linked, as by the dual action of epinephrine, which controls the sympathetic discharges and yet may also initiate the release of adrenocorticoids by stimulation of the hypothalamus.

Samter's patients had an increase in breathing reserve accompanied by an increase in tolerance to histamine following injection therapy with ACTH. It should be pointed out that although his facts and speculations are interesting and suggestive not all patients given ACTH therapy demonstrate such increased histamine tolerance. He concludes, nevertheless, "deficient, possibly faulty, function of the anterior pituitary or the adrenal cortex can originate the non-allergic type of bronchial asthma and perpetuate the allergic type." If this be true, he states, then ACTH and the adrenocorticoids are effective by restoring a disturbed physiological equilibrium rather than by a drug-like action.

In a second report Segal et al[88] describe their results in six men and fourteen women given twenty-seven courses of ACTH (240 to 900 mg), with an initial dose of 40 mg and the same dose six hours later with 20 mg q. i. d. until a maximum benefit has been observed for two days with 20 mg t. i. d. for one to two days and, thereafter, q. 12 h. for two to sixteen days. In these patients, if an adequate eosinopenia did not develop after 100 mg had been injected the dose was increased.

These patients had suffered from bronchial asthma for one to thirty years. No correlation was found between the control eosinophil count and the dose of ACTH needed to produce eosinopenia. All presented subjective improvement one to three days before objective signs of amelioration were seen. Following eighteen courses of treatment, immediate or complete remission occurred with good results in three, fair in four, and none in two. In six patients remissions lasted for more than four weeks, in six more from two to four weeks, and in ten from one to two weeks. In three patients the remission lasted one week. One patient is still in remission after seven months. Almost all of the patients required supplementary medication, although its amount was strikingly reduced. Medical treatment consisted of rectal aminophylline, Hydryllin, or potassium iodide. An attempt to prolong the remission by the administration of ascorbic acid orally or intravenously in doses of 4 gm/day failed. Continued administration of ACTH (10 to 20 mg/day) did not maintain the remissions of two patients. In one subject the side reactions included dyspnea, orthopnea, cyanosis, confusion, and non-responsiveness on two occasions. Two individuals refractory to ACTH failed to respond to cortisone, but a third, who was unrelieved by cortisone, subsequently responded to ACTH.

In a series of studies concerned with the effects of ACTH in bronchial asthma, Segal and Herschfus[89] reviewed the subject in both its clinical and laboratory aspects. Almost all of the clinical papers listed by these authors have been abstracted for a second time in order that the present review might be more complete. The second half of their review as concerned with the studies of the mode of action of ACTH and the nature of the immune reactions noted is too succinct to permit synopsis and should be read in the original. Their conclusions merit repetition and emphasis. They speak of the exact mechanism of the action of ACTH as yet not understood, although therapeutic benefit is probably achieved by creating a state of hormonal excess, inhibiting the altered reactions of

cells probably at the mesenchymal level. At the time this paper was published, they felt that prolonged administration with ACTH was not feasible and that there was some evidence that in relapse the symptoms of some types of hypersensitivity might recur with greater severity. In any case, repeated stimulation of the hypothalamus-pituitary-adrenal axis may not be desirable. It remains to be revealed to what extent the undesirable physiologic toxic effects of ACTH may limit its usefulness in the treatment of chronic allergic disorders.

In a later communication, Segal, Herschfus, and Levinson[40] summarized the results of twenty-seven courses of therapy administered to twenty patients over a period of eight months. All of the patients suffered from severe bronchial asthma, and following all but two courses there was complete or partial remission. Only six of the patients, however, were able to discard all supplementary medication. The first symptoms to disappear were the paroxysms as manifested by cough, râles, and inspiratory wheezing. In the authors' experience, short intensive courses of therapy are more effective in the long-term management of severe bronchial asthma patients than are the attempts to prolong the initial remission with daily "maintenance" therapy of one or two doses of 20 to 25 mg. One patient, however, suffering from an associated rheumatoid arthritis, has taken 30 mg daily for a long period of time and has remained free, as well, of asthmatic attacks. The side effects noted include weight gain (which reached a maximum of eighteen pounds in one patient) controlled in those with frank or latent heart failure by rigid salt restriction, digitalization, mercurial diuretics, and potassium chloride. Other side effects include the usual mooning, mild hirsutism, lentiginous pigmentation, transient glycosuria, edema, and euphoria. Several patients complained of a sensation of tightness or mild constriction of the chest one-half hour following injections. During the first three days of therapy, others complained of abdominal bloating and a tendency to constipation. In one patient a nonpruritic erythematous macular rash appeared on the lower extremities. Lasting three to five days, it reappeared during each of three courses of ACTH therapy. Once again, as in the earlier communications, the authors state that they were unable to demonstrate significant protection with a single large dose of ACTH against the broncho-constriction and dyspnea produced by intravenous histamine or methacholine in asthmatic patients. Similar studies have been carried out in several patients during and following a complete course of multiple ACTH injections. The results were variable, although there was a marked decrease in histamine sensitivity. This may be nonspecific, since it has also been observed following improvement in bronchial asthma due to any other therapeutic program. Skin test reactions and passive transfer studies were unaltered. The authors stress the fact that "the uncontrolled use of such a powerful therapeutic agent should be discouraged."

In their most recent communication[41] (December, 1951), Segal and Herschfus report on the use of ACTH given intravenously for the treatment of bronchial asthma. The patient is started on a continuous infusion of 5 per cent glucose in distilled water for a total of 3 liters/twenty-four hours at the rate of 30 drops/minute, usually with 0.5 gm of aminophylline in each liter of fluid. The ACTH is added to the extent of 10 mg/L for a total dose of 30 mg/day. After the second day of continuous ACTH intravenous therapy, the drug is administered only in the first liter of fluid daily, although the infusion of glucose with or without aminophylline is continuous. As improvement occurs, the dose of ACTH is decreased

to 10 to 13 mg/day. The treatment period varies from one to nine days and the total dose from 10 to 210 mg ACTH. In all, seven patients became symptom-free for a variable length of time followed by partial remission thereafter. In three patients there were partial remissions, but, in all, there were no complete therapeutic failures. In one patient a severe recurrence occurred eight weeks after the intravenous treatment, and in another in three weeks. Good partial remissions have been observed, however, up to eight weeks. Intravenous treatment has the advantage of obtaining a more rapid therapeutic effect maintained throughout the twenty-four-hour period. The total dose needed varies from one-fifth to one-eighth of that required intramuscularly. Resistance to intramuscular ACTH may be overcome by intravenous administration. The same physiological effects are noted as with intramuscular injections. It is not certain from this small series of cases that the duration of hospitalization is shortened by this type of treatment. All of the patients received concurrent penicillin or aureomycin to protect them against the possibility of greater susceptibility to infection. The same persistent type of bronchitis seen in patients taking intramuscular treatment was observed in those taking ACTH intravenously. This generally responded to intensive antibiotic therapy, iodides, and antihistaminic agents. In two patients febrile episodes, the pathogenesis of which could not be determined, occurred. In this series recurrences were delayed by the concomitant administration of large doses of oral or rectal aminophylline and antibiotic medications. The case histories are reported in detail and are worthy of careful study.

Seibold[42] used ACTH in forty-one patients suffering from various allergic diseases. The best results were, as usual, obtained in those with disorders of self-limited duration, such as penicillin reactions. In patients with severe bronchial asthma, symptoms recurred within three weeks after the treatment was discontinued. The most remarkable improvement occurred in patients with seasonal hay fever, and the poorest results were noted in cases of atopic eczema. The authors suggest that ACTH and cortisone should both be used with the utmost caution in allergic disorders, at least until their mode of action is understood.

In all, Sherman[43] administered ACTH to approximately fifty patients presenting an intrinsic type of bronchial asthma, many of whom also suffered from vasomotor rhinitis. Concomitant medication such as epinephrine, aminophylline or Demerol was continued as needed. Improvement with decrease in need for symptomatic medication was usually apparent by the third or fourth day, and all the patients were essentially free of asthma by the tenth treatment day. Polyps were decreased by the fourteenth day. Recurrence was noted within a period of two to sixty days after cessation of treatment. The side reactions seen during the treatment period included a toxic psychosis in two patients and moderate fluid retention and mooning in about 10 per cent of those studied, with hirsutism occurring in one child. The initial doses varied from 20 to 25 mg q. i. d. reduced after two to three days of treatment to 10 to 12.5 mg q. i. d. for 7 to fourteen days. In children the dose was halved.

Spies and Stone[44] studied a number of clinical syndromes as affected by ACTH. Among other disorders their patients suffered from asthma, hay fever, urticaria, and chronic eosinophilia of unknown origin. Prompt and dramatic improvement is reported as following the repeated injections at dosage levels of 25 mg. They conclude from their studies that they do not know why ACTH relieves the symptoms of rheumatoid arthritis, gout, asthma, hay fever, urticaria, or psoriasis, or why the circulating eosinophils

decrease in number after its administration. They feel that ACTH is a tool of clinical and laboratory research and that the results so far achieved are merely clinical leads for further experimental studies.

Thorn,[45] who with his associates carefully reviewed the use of ACTH in a number of syndromes, treated as well three patients with severe chronic bronchial asthma, using doses of ACTH (10 mg q. 6 h.). The remissions lasted from five to seven days after cessation of therapy. In one patient no recurrence occurred for one month. He considers that ACTH is the drug of choice for patients who have ceased to respond to the usual therapeutic measures, and that, furthermore, the therapeutic effects of other more common treatment agents may be restored during the ensuing remission.

What are the effects of ACTH on other chronic pulmonary conditions? West and his colleagues[46] studied three patients with impaired alveolar capillary gaseous diffusion which, in the first patient, was caused by fibrosis due to scleroderma; in the second, to a pulmonary granulomatosis of unknown etiology; and in the third, to an unknown cause. The first patient received cortisone, 100 mg daily increasing to 150 mg during a period of nineteen days, with no change in pulmonary dysfunction. The second patient received a daily dose of cortisone, 100 to 300 mg to a total of 4 Gm over a period of seven weeks, with subjective improvement, a decrease of effort dyspnea, some regression of radiological abnormalities, and a decreased cellularity as noted in biopsy material. The improvement was sustained for a follow-up period of approximately two months. In all three patients the respiratory functions studied included spirometry and determinations of maximum breathing capacity, arterial oxygen saturation, dead space, venous admixture, oxygen-diffusing capacity, and pulmonary arterial pressures. The third patient was given ACTH (100 mg daily), the doses reduced later to 50 mg daily, with dramatic improvement. The treatment was continued with cortisone, the maintenance dose being 50 mg three times weekly. The pulmonary dysfunction disappeared and the patient has remained well.

In the papers listed above, Segal notes the similarity of bronchial asthma to other "alarm reaction" patterns and mentions the possibility that the patient's response to ACTH may be due to the effects of the hormone upon stress. In a separate communication Winer, Beakey, and Segal[47] discuss the clinicopathologic relationship of bronchial asthma with consideration of its part in the general adaption syndrome. Although Selye and others have reported that bronchial asthma is one of the adaption syndromes, this paper, which is not concerned with ACTH, should nevertheless be part of a review of its properties. The study concerns the post-mortem records of forty-six patients, approximately one third of whom died in an attack of, or because of, bronchial asthma. The second group, although asthmatic, had died from one or another of its complications. The third group consists of asthmatic patients who had died from intercurrent or unrelated disease. To a varying extent, all of the patients with bronchial asthma showed changes in the lymphoid and endocrine tissues consistent with a reaction to stress, with apparently successful adaptation. Similar, as is generally known, are histological changes seen, as well as the result of successive responses to histamine, epinephrine, anoxia, and alarm. Changes of this type were most marked in those patients who had died in an attack of bronchial asthma and were much less prominent in patients of other groups.

ACTH having been administered intramuscularly and intravenously,

it was only natural to expect that attempts would be made to use it locally by aerosolization directly to the lungs. Zanartu[48] in this manner treated six normal and three asthmatic patients. The degree of absorption was measured by the lowering of the numbers of the circulating eosinophil cells as determined hourly for three to four hours following inhalation. The solution used contained 32.5 mg of ACTH in 2 cc distilled water, the entire amount given in a single dose using oxygen at a pressure of 5 to 7 pounds/sq. in. as a propellant. The response was in all nine cases similar to that seen following intramuscular injection. The greatest decrease in circulating eosinophil cells was observed during the first and second hours after aerosol administration. The only side effect noted was transient moderate salivation.

If it is at all possible to summarize our knowledge at this point, we can only say that the usual pattern of response following the use of ACTH in pulmonary spastic disorders is a dramatic improvement with substantially complete, if not almost complete, temporary remission of all of the signs and symptoms of bronchospasm. The period of freedom from symptoms may last from several days to some weeks and in otherwise well patients for some months, granted that the causative allergens are eliminated. Continued treatment with small doses of ACTH does not seem to be indicated, although there are patients with concomitant conditions who require such treatment and whose asthma is thereby much improved. In many patients the improvement is so great that milder medications can be used to control such symptoms as may appear. In ACTH we have a drug with which symptomatic relief can often be quickly achieved. It must be stressed, however, that all of the studies so far done point only to one fact: that we are really not much farther along the road to a solution of the problem of bronchial asthma. If the drug has not lived up to either its first promise of relief given or to its first threat of dangerous side effects, those effects seen in the first patients treated are now considered to be minimal and easily controllable. The allergist who practices internal medicine will find himself using ACTH more and more frequently in the treatment of asthmatic patients while the basic studies and hyposensitization treatment for which ACTH is no substitute are in progress.

ACTH AND THE NOSE

In the beginning, ACTH was much too scarce and relatively too expensive to be used for patients suffering from nasal disorders. The first reports of its effects upon the nose were, therefore, incidental to the treatment of other syndromes. In some reports bronchial and nasal allergy, as differing aspects of a single sensitivity, are listed together. The references, therefore, overlap. In the present review they are discussed separately in order to facilitate further study. Some of these have been recently reviewed in the last issue of ANNALS OF ALLERGY, not available while this review was being prepared.

In his first report in 1949 Bordley and his associates[49] noted that in three asthmatic patients with edematous, purulently discharging nasal mucous membranes, the edema subsided, although there was no gross change in the volume of the lymphoid tissue present. In two patients obstructing nasal polyps almost completely disappeared. In one patient several small polyps reappeared twenty-three days after the discontinuation of the ACTH. In one patient skin sensitivity to pollens and other extrinsic antigens was greatly diminished during the treatment period

but returned to its original level in three weeks. In another patient sensitivity to extrinsic antigens was not affected. In two patients intradermal reactions to bacterial antigens decreased significantly, permanently in one case and temporarily in the other. In one other patient such skin tests were unchanged.

In a second report Bordley[50] described the tissue changes seen in the upper respiratory tract of forty-seven patients given ACTH. In all, 400 examinations were done, nasal polyps being removed from five patients and nasopharyngeal lymphoid tissue in sixteen others. A total of forty-seven biopsies were performed at varying intervals during the treatment period. Routine studies included palpation of the lymph nodes and inspection of the mouth, tongue, and throat with transillumination and roentgenoscopy of the sinuses. The author states that during the treatment period the nasal mucous membranes shrink, develop a slate-pink color, and are covered with a thin layer of clear mucus. Polyps become opaque and pink and begin to shrink, in many cases completely disappearing. The nasopharyngeal lymphoid tissue becomes clearly delineated from its surrounding stuctures, developing an orange-pink color. Some days after the cessation of treatment the nasal mucosa loses its dusky appearance, and the lymphoid tissue returns to its former state. It takes from two to eight weeks for the nasal polyps to return.

In a third report Bordley[51] described the tissue changes seen in the upper respiratory tract of more than sixty patients suffering from a number of allergic and nonallergic disorders. In these the results of the previous studies were corroborated; and, in addition, it was noted that atrophic crusts and ulcers cleared or improved. Fifteen patients with polyps or polypoid changes, with or without allergic asthma, responded with diminution, if not complete disappearance, of polyps after two weeks of treatment. No uniform changes in lymphoid tissue were observed on twenty-six biopsies from sixteen patients and on twenty-one nasal polyp biopsies from five patients, one of whom was treated with cortisone.

Feinberg, Dannenberg, and Malkiel[52] reported that three patients with hay fever were questionably relieved with one or two courses of 250 to 1010 mg of ACTH in three to twenty-nine days. The report states that nasal and ophthalmic reactions in patients with nasal and conjunctival allergy were not significantly altered. Sensitizing antibodies were not affected by either ACTH or cortisone. On the other hand, the Friedlaenders[53] reported that the administration of ACTH every six hours for one week frequently alleviated severe hay fever symptoms for the remainder of the pollen season. Single daily injections were disappointing. In a later report the Friedlaenders[54] wrote that the results of hormone therapy were good in eleven of thirty-two patients with severe hay fever, fair in three, and poor in eighteen. The dosage schedule followed consisted of the daily administration of ACTH (100 mg) with gradual reduction in dosage after three to eight days or as soon as improvement occurred.

Hench et al,[55] reporting on the use of ACTH in rheumatoid arthritis and other conditions, mention that coincidentally hay fever was benefited in two patients. One patient with bronchiectasis and one with chronic neurodermatitis were each also improved during such concomitant treatment.

Koelsche et al[56] in their first report described twelve patients, varying in age from twenty-six to sixty years and suffering from nasal allergy, who were given ACTH (25 mg q. i. d. for two to fifteen days). In six or seven sensitive to ragweed pollen, moderate to marked symptomatic

relief occurred, generally lasting two to three days. In one, little relief was noted, probably due to inadequate dosage. Five individuals who had suffered from severe and continuous vasomotor rhinitis for one to twenty-eight years noted marked symptomatic relief within periods of time varying from a few hours to three days of ACTH administration. In some cases the remission lasted up to five weeks. Nasal polyps shrank approximately 50 per cent, and no undesirable symptoms or manifestations were seen.

In a second report Koelsche and his colleagues[57] described among others seven patients with hay fever who achieved moderate to marked relief lasting only during the treatment period or for a few days more, and five others with vasomotor rhinitis who were markedly relieved for some time after cessation of treatment. A study of the data shows that some of these patients were treated toward the end of the ragweed season and that some of the relief may have been due to a diminution in the amount of pollen to which they were exposed.

The ten patients studied by Leith, Graham, and Burrage[58] varied in age from twenty-one to forty-four years and suffered well-defined symptoms of pollen hay fever with positive pollen skin tests. Following treatment with ACTH (20 mg q. 6 h.) in four patients, the hay fever symptoms temporarily disappeared. In one patient who presented wheezing there was no amelioration of the bronchospasm. It is noted that reactions to skin tests were diminished in four patients, abolished in one, increased in one, and unaltered in four more. The passive transfer phenomenon showed diminution in two patients and an increase in three after ACTH treatment. In the others the skin tests were unaffected.

Massell and his group[59] gave their patients with hay fever ACTH (25 mg q. 6 h.) for two days. They state that the patients were completely relieved of attacks for the remainder of the season. Randolph and Rollins[60] reported that striking results were obtained with ACTH treatment for hay fever due to ragweed. It not only eradicated all symptoms of hay fever but also, as with Massell's patients, gave protection for the rest of the season. These authors also used doses of 25 mg q. 6 h.

At the first clinical ACTH conference the same authors[61] described four patients with acute ragweed hay fever hospitalized for a period of one week between August 31 and September 11, 1949. For two days before starting ACTH treatment, the daily incidence of coughing, sniffling, and sneezing was recorded. During this same period of time, hospitalized-control untreated patients were observed to have severe hay fever. During the first hour after the initial intramuscular injection of ACTH, 25 mg, the patients noticed an increased ability to breathe through the nose, a partial relief of the rhinorrhea, and a lessening of the toxic or constitutional symptoms of pollinosis. The treatment was continued at six-hour intervals for twenty-four hours in one patient, for forty-eight hours in two more, and for fifty-six hours in the fourth. Two patients had never previously received specific treatment with ragweed pollen extract, and two others had been treated preseasonally, the injections having been stopped one month prior to the administration of ACTH. Two of the patients continued without hay fever symptoms for the remainder of the pollen season, and one had a recurrence of mild hay fever the fourth day following cessation of treatment. One patient had complete relief not only of her perennial nasal allergy and allergic headaches but also of her food sensitivities.

The studies done by Rappaport and his colleagues[62] were much more

carefully controlled. In all, thirty-four patients were the subjects in the experiment, eight being selected at random for placebo injections. In seven, asthma was a complicating disorder. Of the remaining twenty-six patients, of whom twenty suffered from asthma and six from nasal allergy (all sensitive to ragweed pollen), nine showed clinical improvement following the injection of 60 mg of ACTH daily for four days. None of the eight patients given placebo injections was improved. Neither the skin sensitivity to ragweed pollen nor the reagin titer was altered by ACTH treatment. Edema and eosinophils in various stages of disintegration were found in the pretreatment, posttreatment, and control biopsies.

In an extension of the pilot experiments started in 1950, Rappaport and his colleagues[63] showed that mucosa obtained by biopsy and stained by routine methods failed to show histological differences in the tissues before and after ACTH therapy. Thirty of the patients of the series studied in 1950 and sixteen more were available for further observation. In addition, sixteen were given no treatment and served as controls. The authors state that "the major changes observed in the mucosa obtained at the end of four days of treatment with ACTH when compared with that removed before treatment were: (1) an increase in the cement substance between epithelial cells, shown especially in the interepithelial cement of mucous glands, (2) an increase in the number and size of secretory granules in the mucus-secreting glands, (3) an increase in the staining density and in the width of the submucous and of the perivascular 'basement membranes,' (4) an increase in the thickness of the individual fibers of the ground substance, (5) an increase in the number and size of red staining granules in the cytoplasm of spindle shaped, stellate, oval and round cells present in the submucosa. . . . These findings suggest that in patients with pollinosis who receive ACTH within the limitations of this experiment, there occurs in the nasal mucosa increased activity of immature connective tissue cells indicated by an increase in the formation of mucoprotein granules in the cytoplasm."

Rose, Schwarz, and Franklin as quoted above[64] for their studies in asthmatic patients mention incidentally that six of eight patients with nasal polyps obtained satisfactory results with ACTH treatment. Their paper states, however, that 50 per cent of the patients relapsed within one week after the conclusion of therapy and all but one subsequently relapsed.

Seibold[65] noted the remarkable improvement observed in patients with seasonal hay fever with four to six days of ACTH treatment, several patients remaining symptom free for the remainder of a rather severe season. These same patients had not responded previously to antihistaminic therapy.

As an incidental discovery in a group studied by Sherman[66] note was made that polyps were not visible in the asthmatic patients by the fourteenth day of treatment. In an unspecified number of patients with hay fever receiving both ACTH and cortisone for treatment of other diseases during the hay fever season, definite relief of the allergy was noted during and shortly after treatment. All were given ACTH 20 to 25 mg q. 6 h. for two to three days, and thereafter, 10 to 12 mg q. 6 h. for the entire course of treatment. Side reactions were seen in fewer than 10 per cent of the patients followed.

Although the group of patients studied by Spies and Stone[67] included only one patient with hay fever who was relieved of his difficulties, these investigators are quoted once more because of the conservative conclusions they drew from their studies, which, they say, throw no light on the

mechanism by which ACTH relieves the symptoms arising from the various disorders for which it is used. The studies are, therefore, only clinical leads for further experimentation.

Thorn and his co-workers[68] reported as part of their general review that one of their patients who had suffered from a severe, persistent vasomotor coryza of two years' duration responded within twenty-four hours after starting ACTH treatment in doses given 10 to 12 mg every six hours for ten days. All signs and symptoms of allergic rhinitis disappeared after ninety-six hours, and improvement had persisted for three months through the period of report.

Zeller[69] studied eight patients with ragweed hay fever and bronchial asthma and noted that one obtained almost complete relief from 12.5 mg and one from 15 mg q. i. d. Of the others given 25 mg q. i. d., all but one, who was completely relieved, continued to have hay fever of mild to moderate severity. He stated that it appeared from his work that an initial dose of 25 mg q. i. d. was not excessive and that a maintenance dose of 15 mg was necessary. In general, the asthma was relieved more quickly and more completely than the pollinosis. During the pollen season Zeller's patients presented a relief which lasted up to three to five days. Non-seasonally, amelioration lasted up to four months after cessation of ACTH therapy. He noted no side reactions with the doses given.

All we can say from study of the published material is that a good number of the patients with nasal disorders benefit from a course of ACTH treatment. In those in whom the basic sensitivity and exposure are of seasonal or environmental nature, the remission may, of course, last until the next seasonal exposure. The remission cannot in these cases, however, be termed as due to hormone treatment. In some of the patients studied by the present reviewer, symptoms recurred within forty-eight hours after discontinuing the drug. For the moment, hypersensitization with specific extracts of known potency remains the only consistently successful method of treating nasal allergy. In patients suffering from vasomotor coryza who do not react to the standard procedures, a short course of ACTH treatment would certainly seem indicated.

ACTH AND THE SKIN

In correlating the data concerned with dermatologic allergy, we are once more faced with the problem which arose in reviewing the effects of ACTH upon pulmonary and nasal allergy. A number of the reports deal with all three. In order to whittle the subject down to a reasonable size, it was considered more practical to segregate the bibliographies concerned with each aspect of the subject, although this might necessitate some overlapping and occasional repetition.

In discussing the effects of ACTH upon dermatologic allergy, it is necessary to emphasize the results seen following the administration of ACTH in skin conditions as well as the effect of ACTH on the skin itself.

Baldwin and de Gara[70] studied four male and four female patients whose eczema had been present from one month to nineteen years. Extrinsic sensitivities were present in six patients, chronic infectious foci were demonstrable in five, and an abnormal psychosomatic background was considered as present in four. Concomitant allergic diseases such as hay fever or asthma were present in five of the eight patients. As in the asthmatic patients studied at the same time, satisfactory symptomatic relief was the rule on an average daily dose of ACTH, 400 to 1130 mg for five to twenty-five days. Excepting one patient who presented a case of

acne, there were no serious complications or side reactions. Following the hospitalization period, five patients were treated on an ambulatory basis, and of these only one has been able to discontinue the use of either ACTH or cortisone without serious recurrence. Upon returning home, complications attributed to the drug occurred in three patients: in one the severe acne mentioned above; in a second, glycosuria; and in a third, temporary depression.

As part of the study, it is stated that in ten patients with clearly defined inhalant sensitivity by clinical history and positive skin tests, reactivity to the specific antigens persisted despite prolonged treatment with either ACTH or cortisone, and was usually as strong as before hormone therapy was started. The authors stress the fact that both ACTH and cortisone generally improve the attitude of patients with asthma and eczema toward their disease. The failure of therapy as directed solely to the psychosomatic aspect of these conditions is contrasted with the improvement manifested with ACTH and cortisone, indicating that the constitutional pattern of the disease is not directly approachable through psychosomatic channels alone. They suggest that the therapeutic effect is due to a temporary change in the underlying pattern of constitutional reactivity.

Behrman and Goodman[71] noted skin complications on ACTH treatment in the skin as observed in four patients, the first three with lupus erythematosus and the fourth with a recurrent type of skin eruption diagnosed as erythema multiforme. On the twelfth day of treatment the first patient presented an acneiform eruption involving the face and shortly afterwards striae on the abdomen, with purplish striae appearing on the arm on the twenty-eighth day of treatment. Mooning occurred on the thirty-fourth day after initiating ACTH injections, which were started with 100 mg daily and gradually decreased to 40 mg by the eighth day. The second patient received ACTH, 100 mg, for five days, and then 50 to 75 mg daily for the following two weeks. On the fifth day of treatment the facial erythema began to fade, and a brownish pigmentation appeared on the upper lip. By the twentieth day of treatment there was a deep pigmentation of the original area and the surrounding skin. At the same time, there was a hypertrichosis of the chin and the upper lip. The patient who suffered from a decubitus ulcer and a wound from a cutaneous biopsy presented a loss of healing power, with the presence of hyperpigmentation occurring around the edges of the wound. In the third patient, the acneiform eruption began about forty-two days after treatment was started; while in the fourth patient, a generalized pigmentation began on the seventh day of treatment, especially around the site of the skin lesions and a biopsy site. This deep biopsy area, which was one week old, opened on the fifth day of ACTH treatment therapy. It showed no signs of healing, and granulation tissue was completely absent. The patient who had a number of large keloidal scars noted that they became completely flattened and softened. Three days following cessation of treatment, granulation tissue appeared at the biopsy site which subsequently healed. The authors list the mechanisms by means of which such effects might take place.

The report by Brodthagen[72] is worthy of comment because this worker and his colleagues treated nine patients with various skin conditions, obtaining favorable results in pemphigus and psoriasis but not in periarteritis nodosa, the patient showing no clinical improvement whatsoever following twenty-two days of ACTH treatment. The dose varied from 10 to 45 mg/day. Side effects seen were hirsutism and slight acne in one patient, delayed healing time in another, the development of small areas

of edema in three, and scanty premature menstruation in two. Although other workers stress the euphoria seen in patients treated with ACTH, Brodthagen notes how remarkably tired and apathetic several of the patients became after cessation of treatment.

Other papers on the effects of ACTH on skin disorders should be read, keeping in mind the side effects of ACTH on the skin. Studies by Brunner[73] working with Riddell and Best describe hyperpigmentation as occurring in nineteen of forty-one patients treated for fourteen days or more, and in none of twenty-four patients treated for fewer than fourteen days. Acne occurred in seventeen of the first group and in none of the second; mooning in eleven of the first group and in none of the second; hypertrichosis in seven of the first, and in one of the second; and seborrheic dermatitis in one patient in each group. The authors give a detailed case report of an unusually severe cutaneous reaction to ACTH and suggest that these findings confirm the causative importance of endogenous steroids in the production of acne vulgaris and seborrheic dermatitis.

The effects of ACTH and of cortisone on drug hypersensitivity is reported by Carey and his group,[74] who treated thirteen patients in all. One of these was sensitive to iodine; five had the serum sickness type of reaction to penicillin. Another had acute symptoms of sensitivity to atropine, and one other, a reaction to sulfadiazine. One patient who was sensitive to sulfapyridine responded temporarily, although the patient subsequently died of uremia. Sensitivity to acetylsalicylic acid in one patient who presented intractable asthma was considerably decreased by large doses of ACTH. In one patient with paroxysmal hemoglobinuria with development of urticaria of the foot following chilling, the reaction was blocked by ACTH administration, but the antigen-antibody reaction with hemolysis of the red cells was not interfered with and the cutaneous reaction to histamine was not altered.

Cooke and his co-workers[75] studied eleven patients with intrinsic allergic dermatitis, eczema being present in six adults and five children. In addition, ACTH was used in one patient with generalized extrinsic dermatitis due to Furacin. The skin cleared in three days, remaining in remission. Pruritus was the first symptom to decrease, and in acute cases the skin texture rapidly returned to normal. Pigmentation cleared more slowly, but lichenification resisted treatment. Cessation of ACTH therapy was followed by a rapid return of the symptoms in all eleven cases of intrinsic origin. In five cases of urticaria, relief followed ACTH therapy in three to five days, but the drug had no lasting effect unless the cause of the skin response was discovered and removed.

DiGeorge and Nelson[76] feel that ACTH has no place in the therapy of infantile eczema, excepting possibly as a temporary adjunct during periods of unusual stress, although the drug caused a remission in three infants aged two, five, and seven years, within twenty-four to forty-eight hours following doses of 5 to 8 mg q. 6 h. Relapses recurred generally within a few days after the discontinuation of treatment. Remissions could be produced by second or third courses of treatment. In one instance an attempt to prolong the remission by giving small doses of ACTH once or twice daily did not prevent relapse. There was no evidence of untoward effects of ACTH on the infants treated for the short periods of time described in this study.

Recently a complete review of the use of ACTH and cortisone in dermatology has been published by Downing,[77] whose paper should be studied for its details on the effect of these hormones on a number of skin dis-

orders. Worthy of note is one of Downing's own patients who suffered from a severe exfoliative dermatitis of over two years' duration. At first, treatment with both ACTH and cortisone brought prompt results. After each course of medication, however, the eruption promptly recurred, and each time the dosage had to be increased. The patient is still suffering from his exfoliative dermatitis and, in addition, has now developed marked psychotic disturbances necessitating hospitalization. He continues to receive the hormones, because each time treatment is discontinued, his eruption recurs. Downing quotes with approval a statement read by Kierland of the Dermatological Staff of the Mayo Clinic before the Section on Dermatology of the American Medical Association in June 1951. Listing the number of dermatological lesions for which both ACTH and cortisone have been administered, he states that from an analysis of their results these hormones are recommended on the basis of the relief of symptoms and not on the basis of cure. Although worthwhile results have been obtained in some cases of exfoliative dermatitis, drug and serum reactions, and the intense pruritus of some eczematous states, nevertheless, these hormones should not be administered promiscuously without knowledge of their physiological effects and dosage and without knowledge of the influence of infection upon those receiving such treatment. With this opinion, the present reviewer heartily concurs.

Etteldort[78] reports on his experiences with ACTH and/or cortisone given to patients with infantile eczema. One of the patients had no relapse in three months following therapy. One patient had beneficent results lasting from ten days to two months before exacerbation occurred. Some of the patients were re-treated with ACTH or cortisone one or more times with temporary improvement. Some had been maintained on daily doses of 25 to 100 mg cortisone for periods of three to twelve weeks.

Evans[79] reports on a remission in idiopathic thrombocytopenic purpura during the administration of ACTH. Feinberg and his co-workers,[80] reporting on the use of ACTH and cortisone in a number of allergic manifestations, note that a case of bullous urticaria due to penicillin subsided following ACTH administration but recurred ten days later, when it responded to a second course of treatment. The total dose given was 630 mg over a period of nine days. One of their patients who presented a severe urticaria and angioneurotic edema responded to an initial course, but the signs of the condition recurred within a few days following cessation of treatment. The authors state, and wisely, that in acute lesions the chances of coincidental spontaneous remissions makes the interpretation of favorable hormone results hazardous.

As regards the effect of ACTH in pruritus of any type, the remarkable communication by Fromer and Cormia[81] should be mentioned. These investigators studied four patients with chronic intractable anogenital pruritus previously treated with local medication, antihistamines, x-ray, mercurial tattooing, alcohol injections, and vulvectomy, all of which were completely ineffectual. In one patient with a dosage of ACTH initially 100 mg daily gradually reduced to 10 mg, the pruritus was completely gone in seventy-two hours. The remission has so far lasted for four months. In a second patient, the remission occurred in forty-eight hours and has so far lasted for three months. In the third case the pruritus subsided gradually over a fifteen-day period, and the remission has so far lasted five months; while in the fourth case freedom from pruritus occurred in forty-eight hours but returned with its original severity in two months.

No rationale for the success of ACTH therapy in this syndrome is given.

Gay and Murgatroyd[82] used ACTH in oil for eight patients. Four suffered from contact dermatitis due to medication, and four others were sensitive to poison ivy. The amount of ACTH required to relieve contact dermatitis averaged 220 mg administered in two to six doses, one injection daily. The authors laud the economy, the convenience, and the gratifying results seen following the use of ACTH in oil or gelatin media.

The five infants and children studied by Glaser[83] had previously resisted all other efforts directed at relieving their atopic dermatitis. Good, although temporary, results were obtained in all skin conditions, although one patient developed a nephrosis requiring discontinuation of the treatment. One female infant developed a transient hypertension. One patient with a depressive psychosis considered due to the eczema was treated successfully. The author feels that hormone therapy should not be used until all other orthodox types of treatment have failed. He emphasizes the importance of protecting the patient against infection during periods of ACTH therapy. He found ACTH useful in clearing the skin so that direct skin testing could be done, although in each case this corroborated the results of previous testing by the passive transfer method.

Although Hampton's report[84] is chiefly concerned with the clinical effectiveness, practicality, and economy of intravenous ACTH treatment, it is included at this point because of the fact that a number of the patients studied suffered not only from severe status asthmaticus but also from urticaria, allergic dermatitis, and drug reactions, all responding most gratifyingly and sometimes dramatically to intravenous therapy.

Hestetun and Wennevold[85] describe three cases of atopic eczema treated with ACTH with excellent effect. The skin infection disappeared, the general condition improved, the lymph node swelling in the neck receded, and troublesome itching ceased. No unfavorable effects were seen. The disorder recurred on cessation of ACTH therapy, but the eczematous skin changes in two of the patients were definitely less marked than before treatment, and the condition was better. The authors consider ACTH indicated in treatment of atopic eczema when the eczema is generalized and resistant to local treatment, with secondary infection and dystrophy. The treatment period should be six to eight days. Continuous treatment is not advised.

Irons, Ayer, Brown, and Armstrong[86] discuss the use of ACTH and cortisone in diffuse collagen disease and chronic dermatoses, emphasizing their differential therapeutic effects. Their carefully documented paper is concerned with sixteen patients, in which group there was one case of periarteritis nodosa, one of exfoliative dermatitis, and one of superficial allergic dermatitis. Extensive and careful laboratory studies were done at regular intervals. In the patient with exfoliative dermatitis present for thirty years, cortisone was ineffective and ACTH markedly effective. The patient did not co-operate in taking supplementary potassium, and when the dose was reduced to 12.5 mg daily an exacerbation followed. With cessation of ACTH treatment, cortisone was given in doses of 100 mg daily for nine days with little effect. Control of the dermatitis was regained with ACTH in full doses of 100 mg daily. Because of the patient's disorientation and uncontrolled potassium loss, the dose was reduced. Exacerbation associated with several complications led to death. In the patient with allergic dermatitis, cortisone was again ineffective, and ACTH brought about a marked remission of the rash and other symptoms. In all, the patient received cortisone, 3100 gm, in forty-three days and

ACTH, 1500 mg, in twenty-seven days. The patient with periarteritis nodosa showed a remission in five days and remained asymptomatic. The authors stress the importance of the problems of management and the serious complications of long-time therapy in terms of salt restriction, the use of mercurial diuretics in patients retaining salt and water, the administration of supplementary potassium, and the development of Cushing's syndrome, as well as the psychotic complications of ACTH treatment which were not encountered with cortisone. They suggest that although short-term therapy for two weeks or less with ACTH can be carried out safely under a proper regimen without extensive studies, long-term therapy with the hormone demands laboratory supervision. On the other hand, long-term cortisone therapy is more suitable to general use.

Although Kanee and his co-workers report on a single patient with atopic dermatitis treated with ACTH,[87] their paper is worth reading in detail, because of the excellent studies they were able to do, although limited by the age of the patient, who suffered from a generalized eczema and asthma. The infant, aged fourteen months, spent seven months in the hospital and was discharged as well. The transient intense pallor, listlessness, abdominal distention noted to follow each injection of ACTH have been described above in the section on the effect of ACTH on pulmonary disorders.

Kierland and his colleagues[88] at the Mayo Clinic recently reviewed the use of cortisone and corticotropin in dermatology, listing its effect in a number of skin lesions, including atopic dermatitis and generalized neurodermatitis. In these patients the dose varied from 60 to 100 mg daily, with a reduction as soon as improvement appeared. Responses are described as fairly uniform, consisting of a considerable reduction in the pruritus and, in some cases, almost complete relief. The lichenification gradually diminished during courses varying in length from four to twenty-one days. The majority of the patients experienced a relapse in varying periods of time after withdrawal of ACTH, and no permanent effect on the basic disease could be ascribed to the hormones. Some patients with eczematous lesions experienced a drying effect. A few patients were not benefited by the dosage given above, and one patient was markedly unimproved. The authors state that the patients with neurodermatitis had a tendency to become dependent upon the hormone, and accordingly suggest that such treatment be reserved for patients with intractable symptoms and that courses of treatment be of short duration. In common with all other investigators the authors state their warning as follows: "We wish to re-emphasize that corticotropin and cortisone are powerful in their physiological actions and, hence, cannot be administered promiscuously or without full knowledge of their effects. While physiological side effects are usually transient and reversible such reversibility does not detract from the importance of potential seriousness of such effects. In others words, it is recommended that these hormones should not be administered haphazardly or for reasons of 'something or nothing more to do.' We are convinced that too many times these agents have been given for insufficient reasons and without knowledge of their properties and potentialities."

Lever[89] has also recently reviewed ACTH and cortisone in the treatment of the skin diseases as observed in more than seventy patients. In drug eruptions, ACTH brought about rapid relief of symptoms with relatively small doses of 100 mg daily. One patient with severe urticaria and fever due to penicillin showed great improvement after two days of treatment.

Following its discontinuation on the sixth day there was a recurrence of symptoms on the seventh. After four additional days of treatment only a few urticarial lesions persisted. In another patient with a severe extensive dermatitis following injection of gold sodium thiosulfate, there was an improvement within two days and complete remission after three weeks of treatment. One patient with anaphylactoid purpura, arthritis, and severe glomerulonephritis cleared of the purpura and arthritis, although the kidney lesions did not improve. In contact dermatitis the results were equally good, as seen in one patient with extensive contact dermatitis due to the topical application of penicillin. Remission occurred within one week and no recurrence thereafter. In a patient with poison ivy there was no spreading of the lesion and the edema diminished, but the bullae did not involute any faster than they would have been expected to spontaneously. In a patient with atopic dermatitis the rebound phenomenon after discontinuation of treatment was worse than in most other diseases. The author states that once treatment is started, the physician and patient must be prepared to continue it for a long period of time. In one patient, a one-year-old child, with generalized atopic erythroderma, response to treatment was excellent; but on discontinuance the disease recurred, pneumonia and bilateral otitis media developed, and the child died.

Mandell and his colleagues[90] used ACTH intravenously in a twenty-year-old male suffering from eczematoid dermatitis and angioneurotic edema. With substitution of placebo injections on the third day, relapse occurred, with remission following resumption of the ACTH. A sixty-four-year-old male with neurodermatitis was relieved by continued intravenous infusion of ACTH given over a period of eight to twelve hours daily.

At the 1950 conference on the clinical effects of ACTH, Randolph and Rollins[91] discussed the effect of the drug on a male aged thirty-one who had been subject to atopic dermatitis since childhood. Following the elimination of wheat, he had obtained complete relief from eczema for a period of one year. A recurrence one month previous to ACTH therapy and due to the ingestion of wheat was treated with 50 mg q. 8. h. for two days following an additional experimental ingestion of wheat causing a second exacerbation. Over a period of fifty hours, a dose of 300 mg was administered, with diminution in the pruritus noted in two hours after the initial injection. There was progressive improvement with objective evidence of rapid healing throughout the treatment period and for five days thereafter. During the following week, however, there was a gradual recurrence of the dermatitis, which reached a greater degree of severity than ever previously observed.

Another male patient, aged six, responded with approximately 75 per cent relief as a result of allergic management. With a liberal feeding of corn for a preliminary period prior to starting ACTH therapy, there was an acute exacerbation of the skin lesions. There was a rapid cessation of the pruritus and progressive clearing of the erythema coincident with a course of ACTH injections consisting of 16.6 mg q. 8. h. for the first day, 25 mg q. 8. h. for the second and q. 6. h. for the third day, despite the continued ingestion of corn products during this time. This degree of improvement was maintained for a period of ten days and then reverted to a greater degree of involvement than had existed prior to the first observation.

In a second paper Randolph and Rollins[92] conclude that the use of ACTH in atopic dermatitis is not followed by as good results as those

seen in hay fever and bronchial asthma. In four of their patients the remission lasted two to ten days following cessation of treatment. In one patient the recurrence was less abrupt and the pruritus less severe than that seen during the first ten days. It is stressed once again that the recurrence is at least as severe and in some instances more acute than that present for several weeks prior to the institution of treatment. This degree of severity persisted from one to three weeks and then reverted to the previous levels.

ACTH is undoubtedly also useful in the treatment of serum sickness. Seltzer[93] cites a case of a man who received tetanus antitoxin for an abrasion made by a mechanical saw. He evidently suffered from the accelerated type of serum sickness with headache, nausea, lightheadedness, and a rash and general discomfort occurring within forty-eight hours. With ACTH (25 mg q. 6. h.) the rash was gone within twenty-four hours, following which the dose was reduced to 10 mg. After three more injections, the patient was discharged as well.

As the first of a series of studies on pituitary-adrenocortical functioning in patients with atopic dermatitis, Sternberg and his colleagues[94] studied seven normal-control patients and eight atopic individuals. To simulate conditions of stress, the patients were subjected to control periods of one hour in a hot room, in which the temperature was kept between 100 and 110° F. and the humidity at 90 to 95 per cent. Epinephrine was administered and its effects measured. The studies showed that atopic individuals responded abnormally to the artificially produced stress situation by a rising eosinophil count. The authors suggest a derangement of the hypothalamus or some abnormality related to the adrenal medulla as possible causes of the abnormal responses in atopic subjects. On one patient treated with ACTH, every attempt to reduce the dosage below 40 mg daily was followed by a relapse. In this patient it was suggested that the minimum daily requirement similar to that seen in the insulin needs of the diabetic subject appeared necessary.

Briefly, as a matter of record, Stefanini and his colleagues[95] reported on the therapeutic effects of ACTH in a case of Henoch-Schonlein purpura and Steinberg and Roodenburg[96] on the successful treatment of dermatitis due to chrysotherapy.

Sulzberger and his colleagues[97] have come through with a complete investigation of the patients they studied. Their report in the *Journal of Investigative Dermatology* deals with forty-four patients suffering from nineteen different skin conditions treated with an average dose of 25 mg q. i. d. Three of the patients were atopic, presenting a typical dermatitis. One suffered from nummular eczema. The ACTH did not significantly alter the patch test response to eczematous allergens or the wheal response to intracutaneous tests with urticariogenic allergens. The effects on the tuberculin type of reaction were inconclusive. There was no noticeable effect on the immunologic skin reactions of the eczematoid and erythematous type caused by primary irritants or on the immediate wheal reaction due to a nonallergenic primary urticariogenic agent. Relapse of varying degree occurred in almost all of the patients after withdrawal of ACTH. Side effects occurred in twenty-two patients, in twelve of whom were seen increased localized or generalized pigmentation with mooning in nine, hyperglycemia in two, ankle edema in four, transitory toxic psychosis in two, a multiform erythematous eruption with fever and malaise in one, and mild furunculosis in another.

The published reports referring to the use of ACTH in skin disorders

leave us once more with the same inevitable conclusion. In self-limiting syndromes, or those due to a single exposure to a known allergen (as, for instance, penicillin) when such allergens can be subsequently eliminated, symptomatic improvement may be dramatic and long-lasting. In chronic states, such as atopic eczema or exfoliative dermatitis, recurrences may not only be expected to equal but occasionally to surpass the original level of magnitude or disability. The same side reactions occur as when ACTH is used in the treatment of pulmonary and nasal allergy, and, in addition, dependence approaching addiction may be observed.

ACTH AND THE EYE

Both ACTH and cortisone have been used in the treatment of a number of eye disorders which are not allergic in cause, excepting in the broadest sense of the word. As is generally known, in the field of ophthalmology, the term "allergy" is used to denote both a great variety of syndromes characterized by the usual antigen-antibody relationship, and, as well, by the less clearly defined types of bacterial allergy.

Coston[98] relates his personal experiences with ACTH and cortisone therapy, reporting that they produced very prompt healing in patients with acute chorioretinitis or uveitis. Relapses occurred in the tuberculous patients. Of the two drugs the author prefers cortisone, because it can be used locally. In doses of one drop of a 25 mg/cc solution every three hours during the day and once during the night, this treatment produced rapid healing in all but two of eighty-five eyes with all types of inflammatory or allergic disorders "such as acute purulent conjunctivitis, recurrent epithelial erosions of the cornea, acute eczema of the lids, vernal catarrh, keratoconjunctivitis, corneal ulcers, interstitial keratitis and iritis."

Dickey[99] also used both cortisone and ACTH in the treatment of ocular diseases. The cortisone was used as one drop of a 25 per cent solution every waking hour in twenty-five patients, two of whom suffered from allergic conjunctivitis. These are listed as either cured or improved. One of the conditions seen in the five patients resistant to treatment was atopic dermatitis of the lids. ACTH in doses of 100 mg/day was used in three additional patients who took the injections four times daily for seven to ten days, with remarkable improvement in one patient with optic neuritis and resistance to treatment in two patients with acute chorioditis.

Harvey and his colleagues[100] report on the results of the administration of ACTH and cortisone in two cases of granulomatous iritis, in three cases of sympathetic ophthalmia, in five cases of ocular tuberculosis, in one of vernal conjunctivitis, and in two with uveitis following herpes zoster ophthalmia, with beneficial results in all. Whenever the anterior portion of the eye was affected, cortisone was applied locally. This, of course, did not influence vitreous exudation or changes in the posterior uveal tract.

In contradistinction to the report noted above, Hogan et al[101] stated that cortisone produced a marked improvement in a patient with atopic dermatitis and atopic keratoconjunctivitis. The lesions recurred, however, when treatment was stopped after sixty-four full days of therapy. Subsequent treatment with ACTH failed to stimulate the adrenals, possibly because of inadequate dosage or an impotent batch of material or both. The patient took a second course of cortisone with a satisfactory but more gradual response. In one patient with severe vernal catarrh there was a

prompt, dramatic improvement, with a relapse occurring when the treatment was discontinued. The detailed case reports with several patients suffering from other nonallergic ocular disorders.

Olson and his co-workers[102] treated, in all, fifty-one patients with various eye conditions, of whom thirty-seven received ACTH intramuscularly for one to twenty-one days and fourteen received cortisone for two to seventeen days. It is stated that striking but temporary improvement was observed in one patient with severe vernal conjunctivitis given ACTH. The other disorders were not those usually labeled as allergic.

ACTH and cortisone were both used in ocular inflammation by Rome and his group.[103] In some patients the disorders were controlled by intramuscular injection of ACTH b. i. d. When the relapses occurred, a second state of remission was maintained by subconjunctival injections of cortisone. They list five of six patients with vernal catarrh helped by initial subconjunctival injection followed by topical application. When cortisone was used by instillation exclusively in six other patients with vernal catarrh, the subjective symptoms were relieved and redness and mucus were markedly diminished. The granulations were not affected.

A paper by Scheie et al[104] lists the ocular lesions in which the systemic administration of cortisone or ACTH is encouraging, those in which it is questionable, and those which are unimproved by such treatment. They similarly list the syndromes in which local instillations of cortisone are equally effective or ineffective. ACTH is said to be useful in the treatment of endophthalmitis phacoanaphylactica. On the other hand, cortisone by local installation is said to be helpful in not only endophthalmitis phacoanaphylactica, but also in chronic allergic keratoconjunctivitis, blepharoconjunctivitis and a typical vernal conjunctivitis. They conclude that systemic treatment is of value only for acute self-limiting lesions, and local treatment only for lesions of the anterior segment.

Probably the most complete recent review of the use of the two drugs in the treatment of ocular disease is by Smith and Steffenson[105]. Their paper, which is easily available, should be read for a complete historical review and general consideration of the subject. Highlights of this detailed study include the following important statements: "Certainly, one can say that the number of patients who have remained in remission after the initial course of therapy with either ACTH or cortisone has been small." They quote the paper by Olson. He showed that vernal conjunctivitis regressed markedly during the period of parenteral hormonal therapy, with early relapse taking place after cessation of treatment. They state that "permanent control of this lesion appears highly unlikely in view of its hypersensitivity etiology." The authors make one statement which should receive the widest emphasis. They say, "ACTH and cortisone have already assumed a ranking place in ocular therapeusis. The greatest benefits have been found in their use in early, non-specific inflammatory lesions of the eye. Their availability should not be presumed to lessen the need for both their appropriate use and the proper diagnosis of ocular disease. They are agents of manifold properties; like a two-edged sword, they are capable of curing a diseased eye at the expense of the patient's well-being!!"

Woods[106] also used both hormones in the treatment of fourteen patients with various ocular disorders, using cortisone topically in the treatment of eight additional patients. Five of the fourteen who received both hormones parenterally remained unimproved. Among the nine patients who showed improvement after systemic treatment was one of two with sympa-

thetic ophthalmia due to atropine and one with sclerokeratitis with atropine sensitivity. The other disorders treated were not allergic in the usual sense of the word. The author, however, states that in the majority of the conditions in which the blocking effect on the inflammation was observed, there was some reason to suspect an allergic factor for the inflammatory reaction. Nongranulomatous iritis is believed to be due to bacterial hypersensitivity. The inflammatory phase in tuberculous disease is dependent on a hypersensitivity to tuberculoprotein. There is reason to believe that hypersensitivity of uveal pigment is a part of the symptom complex in sympathetic ophthalmia. He concludes that although ACTH blocks the inflammatory and exudative phases of the anaphylactic and allergic reactions, the evidence indicates that they have no effect on the underlying hypersensitive state.

In a later report Woods and Wood[107] described the action of ACTH and cortisone on experimental ocular inflammation. Both hormones injected parenterally have a profound effect on the inflammatory phase of the hypersensitive reaction, blocking the inflammation and exudation which occur in the ocular protein anaphylactic reaction, the ophthalmic reaction secondary to bacterial allergy, and the focal reaction in tuberculous eyes. They suggest that the accumulated clinical and experimental evidence of the effect of cortisone on ocular inflammation leads one to the belief that such effects may be due to a direct action on the local mesenchymal tissue.

The allergist who sees such ophthalmic conditions only secondarily as part of the general picture of atopy will not find much use for either ACTH or cortisone in this part of his practice. Within the limits of this short review of the available literature is to be found the information he requires. For injection treatment, the dosage levels are the same. The side effects, if anything, are less. The results are no better.

ACTH AND PERIARTERITIS NODOSA

The use of ACTH in periarteritis nodosa has been reported upon by a number of observers, some of whose papers have been listed previously also in this present review. The following references are listed separately because they limit themselves to periarteritis nodosa itself.

Johnsson[108] treated a forty-nine-year-old woman with ACTH 40 to 50 mg daily in divided doses and produced an immediate subjective and objective improvement. When after two weeks of treatment the dose was reduced to 4 mg daily, the temperature rose and the patient began to lose weight, but after one week on the reduced dose a second remission occurred. The patient remained symptom-free during the three months' observation period. It is of interest to note that the agglutination titer to sensitized sheep erythrocytes which had been significantly elevated before treatment returned to normal following ACTH therapy.

Levin and his co-workers[109] did metabolic studies on a patient with periarteritis nodosa for treatment over a period of 145 days. Although the patient was clinically and pathologically improved, cure was not effected, although the physical improvement had been sustained for fourteen months. Eosinophil cells disappeared from the circulation within forty-eight hours and did not reappear until two days after treatment ceased. On doses of 40 mg daily the patient presented a strongly negative nitrogen balance while on a maintenance diet marked by a high protein, high caloric intake. Following each course of ACTH treatment, there was a temporary moderate retention of sodium and chloride followed by an escape from adreno-

cortical control as evidenced by the re-establishment of equilibrium. While sodium chloride was being retained, there was a potassium diuresis. ACTH caused a measured increase in fecal and urinary loss of calcium and phosphorus which did not decrease as the hormone dosage was lessened. It is concluded by the authors that the maintenance of adequately high levels of adrenocortical function seems feasible with relatively small amounts of ACTH, after the gland has been stimulated with sufficiently large priming doses.

In their first report Shick, Baggenstoss, and Polley[140] describe the effects of ACTH on two patients with periarteritis nodosa as given continuous or intermittently for three to eighteen weeks. There was some subjective relief and defervescence within seventy-two hours. The sedimentation rate decreased to normal. Three other patients were given cortisone. In all, partial relapses occurred in five patients when the hormones were withdrawn, with improvement upon resumption of treatment. Two patients given cortisone died in seventy-five and 146 days after treatment was started, despite the initial improvement. The third patient presented a severe progressive hypertension. Following biopsy, signs of complete healing were found; but in the healing process there was fibrous obliteration of the vessels resulting in widespread visceral infarction. The adrenal glands of the patient receiving the large amounts of cortisone were atrophic. In most patients evidence of hypercortisonism was seen, and in the two patients who died there was a profound disturbance of plasma electrolytes due, perhaps, to either the hormone treatment or the coincident renal disease.

In a later report Shick and his colleagues[111] added further details as seen during the more prolonged observation period in the same patients who presented the usual side reactions including mooning, with or without mild acne. These disappeared when the hormone was withdrawn. Six of the patients varied in age from thirty-seven to fifty-one years. The two patients with cranial arteritis were respectively seventy-four and seventy-five years of age. It is noted that peripheral neuropathy in one patient was not significantly improved.

ACTH AND LOEFFLER'S SYNDROME

In 1949 Andrell and his co-workers wrote a brief and enthusiastic report of the dramatic effect of ACTH in the case of pulmonary eosinophilic infiltration. DeZoysa has recently (October, 1951) discussed the differential diagnoses and the relationships between tropical eosinophilia, Loeffler's syndrome, and periarteritis nodosa.

Herbert de Vries and Bram Rose[112] reported on the administration of ACTH to a patient with Loeffler's syndrome and to another with tropical eosinophilia. In both subjects there was a transient increase in total circulating leukocytes, with a marked decrease to virtual disappearance of circulating eosinophilic cells in the patient with Loeffler's syndrome. In the patient with tropical eosinophilia, although the eosinophil cells decreased, the percentage decrease was much less and did not persist. The blood histamine level was within normal limits despite the presence of the high eosinophilia and did not vary with the changes in the eosinophil count.

A report by Vines and Clark[113] concerned a single patient who was much more acutely ill than the average patient presenting Loeffler's syndrome. The patient, at first suffering from pollinosis, gradually developed

perennial symptoms with an intermittent nasal discharge, dyspnea, and a productive cough which developed into a typical bronchial asthma. The symptoms continued intermittently until September of 1948, when they suddenly disappeared, asthma reappearing following a cold in December of that year and in March of 1949. In July of that year following a motor trip to the West Coast, the patient became progressively weaker, developed a nonproductive cough, and moderate dyspnea following which a diagnosis of "E-P syndrome" was made. The patient was given aureomycin, streptomycin and penicillin without improvement. Sulfonamides were without effect. Within twenty-four hours after initiating ACTH 25 mg q. 6 h., the patient showed dramatic improvement. A recurrence which occurred one month later required a second course of treatment. The patient has since remained well. The original paper should be consulted for a full discussion of eosinophilic pneumonopathy (E-P. syndrome) as presented by this case report.

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(To be concluded in the July-August issue.)

News Items

ALLERGY SESSION—AMA MEETING

All members of the College are urged to attend the Session on Allergy which meets in Room 4, Navy Pier, Wednesday, June 11, at 2:00 p.m. in conjunction with the meeting of the American Medical Association June 9-13, 1952, in Chicago. The program is as follows:

Wednesday, June 11, 2:00 p.m.

SESSION ON ALLERGY

Officers of Section:
Co-chairmen—Harold A. Abramson, New York; Horace S. Baldwin, New York
Secretary—Hal M. Davison, Atlanta, Georgia

Psychodynamic Pharmacology of the Treatment of Asthma
HAROLD A. ABRAMSON, New York
The Skin Test and its Diagnostic Value in Clinical Allergy
JOHN M. SHELDON, Ann Arbor, Michigan
Pollen and Mold Allergy in the Southwest
BOEN SWINNY, San Antonio, Texas
Infectious Factors in Pediatric and Adult Allergy
ROBERT CHOBOT, New York
Panel Discussion on ACTH and Cortisone and Their Use in the Allergic Diseases
HORACE S. BALDWIN, New York, *Moderator*

Panel

CARL E. ARBESMAN, Buffalo
AUGUSTUS GIBSON, Rahway, N. J.
ALBERT H. HOLLAND, Chicago
GILES A. KOELSCHE, Rochester
M. MURRAY PESHKIN, New York
BRAM ROSE, Montreal

FIFTIETH ANNIVERSARY OF THE DISCOVERY OF ANAPHYLAXIS

The fiftieth anniversary of the discovery of anaphylaxis by Ch. Richet and P. Portier was held on May 10 at 9:00 p.m. in the Richelieu Amphitheater in the Sorbonne. Luncheons and dinners were given preceding the Jubilee. Following the presidential address Prof. P. Portier spoke on "The Discovery of Anaphylaxis"; Sir H. H. Dale (a Nobel Prize winner) on "The Mechanism of Anaphylaxis"; Dr. C. Heymans (also a Nobel Prize winner) on "Anaphylaxis in Pharmacology"; Prof. Ch. Richet on "Alimentary Anaphylaxis"; and Prof. Pasteur Vallery-Radot on "Anaphylaxis and Allergy in Medicine." M. Jean Sarrailh, Director of the Academy of Paris, was president of the Organization Committee; Prof. Richet was secretary-general and Dr. Bernard Halpern co-secretary.

The Committee of Honor follows:

S.A.S., Prince of Monaco, President
Charles H. Best (Nobel Prize), Canada
L. Binet, Faculty of Medicine, Paris
J. Bordet (Nobel Prize), Great Britain
Sir H. H. Dale (Nobel Prize), Great Britain
D. Danielopolu, Romania
C. Frugoni, Italy
C. Heymans (Nobel Prize), Belgium
B. A. Houssay (Nobel Prize), Argentina
A. Lemierre, President, National Academy of Medicine, France
T. Madsen, Denmark
P. Portier, Institute of France
F. M. Rackemann, U.S.A.
A. R. Rich, U.S.A.
B. Schick, U.S.A.
F. Wittich, President, IAA, U.S.A.

A number of members of the IAA in the United States attended.

Credit must go to Prof. Richet and his associates (1898-1902) for explaining this phenomenon. Although Magendi, Flexner, and Theobald Smith had described these unaccountable reactions, the importance apparently escaped them until Richet and his associates made their observations and gave a lucid explanation of the phenomenon. They advanced two basic concepts at that time which hold true today: (1) a foreign substance which on first injection may be relatively harmless may, on reinjection, become severely toxic, even fatal, when given in the same or even small dosage; (2) an interval of several days must elapse between the first and second injections. All credit should go to Richet as being the founder of experimental anaphylaxis, from which our knowledge of allergy and immunology stems.

AMERICAN ALLERGISTS HONORED IN ZURICH

On Friday, September 28, 1951, Mr. and Mrs. Porter Kuykendall, the American Consul General in Zurich, Switzerland, held a cocktail party at their very beautiful chalet on the lake in honor of the American group attending the International Congress of Allergists. The extremely kind and charming Mrs. Kuykendall entertained the group with a combination of American planning to the very last detail and the most magnificent European charm and splendor. The cocktail party certainly helped to culminate a most memorable occasion in the history of the first international meeting.

Gratitude is expressed to the Hon. Richard C. Patterson, Jr., the American minister, United States Legation, Berne, Switzerland, through whose kind offices and personal correspondence the occasion was crystallized.

The following guests were invited, along with their wives:

Dr. Milton G. Bohrod
Dr. Ethan Allan Brown
Dr. Hal M. Davison
Dr. S. M. Feinberg
Dr. Joseph Harkavy
Dr. Wayne M. Hull
Dr. Merle Moore
Dr. Howard Osgood
Dr. Frank Rackemann
Dr. Nathan Silbert
Dr. Leon Unger
Dr. George Waldbott
Dr. Fred W. Wittich

PENNSYLVANIA ALLERGY ASSOCIATION

The Pennsylvania Allergy Association held its spring session May 17, 18, 19 at Galen Hall near Wernersville. On Saturday, May 17, meetings of committees and the board of regents were held. After the business meeeting on Sunday, May 18, a panel on "Breathing: Normal and Obstructive" featured Drs. Joseph Atkins, Dean A. Collins, Julius Comroe, and Archibald Judd, with Dr. Charles Cleland acting as moderator. In the evening there was a banquet followed by entertainment.

The time Monday morning was given to a panel on "Treatment of Allergic Diseases," covering the following: Dermatology—Dr. John Scully; Allergy, Immunology—Dr. Louis Tuft; Internal Medicine—Dr. Charles Brown; Pediatrics—Dr. Ralph Tyson; Otolaryngology—Dr. John Pfromm. Dr. Earl Vollmer was moderator. Following a lecture by Dr. Louis Tuft on "A Critical View of Some Current Problems in Allergic Practice," a "free-for-all on allergy" with Dr. Hyman Slesinger as moderator concluded the session.

NEW SUBSCRIPTION RATE FOR ANNALS

Because of the increased costs of publishing, the subscription rate for ANNALS OF ALLERGY will be $7.50 per year, effective with the July-August, 1952, issue.

BOOK REVIEWS

HEADACHE. Second Edition. By Louis G. Moench, M.D., Assistant Clinical Professor of Medicine, University of Utah School of Medicine, Salt Lake City. 217 pages, 58 illustrations. Price $4.50. Chicago: Year Book Publishers, 1951.

This second edition of a general practice manual is very practical and gives the information the physician needs to benefit his patient. It effectively points out the pain-sensitive structures of the head and the disturbances which bring about their stimulation. There is a full description of essential clinical facts relating to the various types of headache. In this compact book the author combines his own extensive experience with a combination of brilliant research by noted physicians. Nearly 100 different possible causes of headache, both physical and psychological, are detailed, with time-saving recommendations for solving difficult problems of etiology and treatment. In addition to the listing of the causes of headache, illustrative case reports of the various types of headache augment the value of the text. The author also evaluates the allergic, hypophyseal, vasomotor, and brain pathology theories of migraine etiology and discusses the use of ergot preparations, oxygen and trichlorethylene inhalations, and periarterial infiltration. This manual should be of interest to everyone practicing medicine, since it clearly presents specific suggestions for the treatment of headache.

SYMPOSIUM ON THE INFLUENCE OF THE HYPOPHYSIS AND THE ADRENAL CORTEX ON BIOLOGICAL RELATIONS. 50 contributors, 228 pages, 75 figures, 28 tables. Price $4.00. Basel, Switzerland: Benno Schwabe & Co., 1952. (Imported by Grune & Stratton, New York).

This book covers the entire proceedings of the Swiss Academy of Medical Sciences, September 30-October 2, 1951, at Zurich, which immediately followed the First International Congress of Allergists. Some of the articles are in German and others in English. There are many contributors. The president of the Symposium was Prof. G. Miescher, president of the Swiss Academy of Medical Sciences.

The introductory lecture, "The Adrenal Cortex as a Regulator in Tissue Reactions," was presented by R. Levine, Professorial Lecturer, Department of Physiology, University of Chicago, and associated with the Medical Research Institute, Michael Reese Hospital. This report of Dr. Levine on the action of cortisone and ACTH embraces comprehensive and ingenious work on animal experimentation. The results obtained support the following view of the phenomenon of stress and its consequences. "In the normal animal, a stress stimulus (such as cold, heat, muscle exertion, drugs, et cetera) sets up a train of impulses which reach various areas in the central nervous system. As a result of this bombardment, two main pathways are stimulated. One excites the anterior pituitary gland to the liberation of ACTH and thus the adrenal cortex is stimulated. The other pathway which is excited by stress is the vast network of the autonomic nervous system. The autonomic neurohumours have pronounced actions on the state of the small blood vessels. In the presence of adrenal cortical hormones, the blood vessels react in a well co-ordinated fashion to the 'autonomic' substances. In the absence of sufficient cortical hormones, the small blood vessels react poorly to the same substances, with the result that contraction and dilatation of blood vessels occurs haphazardly and is not co-ordinated with the needs of the various portions of the body. The beneficial effect of cortical hormones seems to be exerted directly in the area of the small blood vessels and not through the mediation of any so-called 'metabolic effect' on the body as a whole." They showed that the adrenalectomized animal may be protected from certain

stresses by the use of drugs which block the action of the autonomic effector substances or which prevent their production.

This is followed by "The Influence of the Adrenal Cortex on Tissue Reactions to Simple Injuries" by Dr. B. L. Baker of the Department of Anatomy, University of Michigan Medical School, which is very well illustrated.

In turn, follows a series of articles on the influence of the adrenal cortex on simple injuries by such authorities as R. Meier and associates, M. Taubenhaus, A. Studer, J. Seifter, and L. L. Layton. This first topic is discussed by several other authorities attending the Symposium. The second topic is hemorrhagic reactions, introduced by G. Schwartzman of New York, followed by excellent discussion. The third topic is the influence of the adrenal cortex on allergic reactions, presented by three groups, one on anaphylaxis, one on eczematous allergy, and another on infectious allergy.

The charts and photographs are excellent, and there is no book in print at the present time which provides so much investigative and clinical research on the influence of the hypophysis and the adrenal cortex on biological reactions.

CURRENT THERAPY, 1952. *Latest Approved Methods of Treatment for the Practicing Physician.* Edited by Howard F. Conn, M.D. 849 pages. Price $11.00. Philadelphia: W. B. Saunders, 1952.

All the sections have been revised and new authoritative contributors have been added—189 this year. The high standards set by the editor of presenting accurate and detailed information without bias are adhered to. The preceding editions have been very popular. The contributing authors have set down their present methods of treatment in brief, original, to-the-point discussions devoid of extraneous material but in exact detail necessary for proper management of the illness; the articles have been revised by the authors just before publication so as to insure inclusion of the latest accepted therapy. Sometimes, such as in allergic diseases, the discussion of the diagnosis must necessarily be an integral part of therapy, but in general only therapy is covered.

There are sixteen sections, including the appendices and index. The sections embrace the infectious, venereal, and allergic diseases; diseases of the respiratory, cardiovascular, digestive, endocrine, urogenital, nervous, and locomotor systems; and diseases of the blood and spleen, metabolism, and skin.

The therapy of the allergic diseases is written by sixteen authorities in their respective fields in allergy. Also included in this section is an annotated formulary of prescriptions useful in the treatment of allergic dermatoses. The appendices and index include a roster of drugs, dosages, conversion factors, tables for making percentage solutions, and a very complete index.

Characteristic of Saunders books, the paper stock, print, and arrangement as well as binding make it a very attractive ready reference volume covering the whole field of current therapy.

PROCEEDINGS OF THE SECOND CLINICAL ACTH CONFERENCE. Edited by John R. Mote, M.D. Volume I—531 pages, 276 figures, 52 tables; Volume II—716 pages, 311 figures, 81 tables. Price $8.50 each. Philadelphia: The Blakiston Company, 1951.

The material from the Second ACTH Conference was so voluminous that it was published in two volumes. Volume I, Research, deals with the more fundamental aspects of ACTH and adrenal cortical function as well as the effects of adrenal corticoids on different tissue systems under varied physiologic and metabolic conditions, either in the normal human being or in different disease states. Volume II,

Therapeutics, covers papers on the effects of ACTH in the treatment of different disease syndromes, although many of the reports contain observations of a fundamental character. An attempt is also made in this second volume to summarize the results to date in treatment with ACTH, in order to obtain a clearer picture of the therapeutic use of ACTH. At the Conference symposia were held on different related disease syndromes in an attempt to arrive at an over-all evaluation. The Conference was kept informal in order to allow a free exchange of ideas, and as a result considerable discussion arose. Although much research has been done during the past two years, it is recognized that not all problems have been clarified.

The forty-nine topics of the Research volume are divided into seven sections, dealing with general adrenal cortical physiology, kidney and electrolytes, nitrogen metabolism, carbohydrate and fat metabolism, vitamin metabolism, adrenal gland and hemopoietic system, and fundamental acute inflammatory reaction: infection, immunology, and hypersensitivity. The Therapeutics volume contains sections on general considerations, metabolic or physiologic defect, malignancy, surgical use, infectious and liver diseases, hypersensitivity, toxins, inflammatory diseases of unknown etiology, and collagen disease.

The diagrams and tables are well prepared; these, with the other invaluable data, are an inspiration to investigators.

ONE LITTLE BOY. By Dorothy W. Baruch, Ph.D., with the collaboration of Hyman Miller, M.D., F.A.C.A. 242 pages. Price $3.50. New York: Julian Messner, Inc., 1952.

Readers of the ANNALS who are interested in the psychosomatic aspects of allergy will recognize an acquaintance in *One Little Boy,* since Kenneth has already appeared in these pages (Ann. Allergy, 9:508, 1951). The book is an expansion of the salient points touched on in the earlier article. Dorothy Baruch was able to grasp the entire picture of the boy's emotions, needs, and problems, because she not only had him in her office for psychotherapy for two and a half years but also had both his parents in group therapy. In this way she could get three points of view each time an emotional crisis arose in the life of the family. The result is a remarkably well-rounded picture which is also fascinating reading.

Since the age of three, Kenneth had had severe asthma which could be only partially relieved by allergic therapy. When he was seven and began to fail in school, he was placed in the care of a psychiatrist, and gradually there emerged the frustrations, hatreds, and fantasies that had caused him to twist back upon himself and express them through withdrawal from school and playmates as well as in a bodily illness. The chief difficulty lay in his parents' lack of adjustment to each other and to life; this in turn stemmed from the wife's rather threatening mother (and Kenneth's maternal grandmother). The reader is uncomfortably aware that the sins of the fathers are indeed visited upon the sons, generation after generation. Kenneth was gradually enabled to express his resentment at his mother's rejection of him and to resolve his antagonism toward both parents into forms that he could handle. The book comes to a satisfying conclusion, with the boy adjusted to school, to playmates, and to life, and with the parents working out many of their personal difficulties. The asthma to date has not recurred.

Dr. Baruch probes into subjects too often taboo and writes of them fearlessly and openly. In the end she relates them to the problems of all children—all adults—and makes a broad application. The writing is somewhat marred by a soap-opera style, but this will perhaps make the book appealing to laymen. It can be well recommended to parents who do not understand the emotional needs and mind-workings of their children and who suffer from too much repression.